FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

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FDA White Oak Campus

Building 31, The Great Room (Room 1503)

White Oak Conference Center

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

Call to Order

Introduction of Committee

DR. SMITH: Good morning, everyone. If everyone could please take their seats, we can get started. And I would like to remind everyone present to please silence your cell phones and other devices if you've not already done so. I would like to also identify the FDA press contact for this meeting, Ms. Stephanie Yao. If you are here, please stand.

Okay, in the back.

DR. SMITH: My name is Malcolm Smith. I'm the acting chairperson for today's meeting. I will now call this meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee to order. We'll start by going around the table and introducing ourselves, so let's start on the right.

DR. FINGERT: Good morning. I'm Howard Fingert. I'm a medical oncologist/hematologist. I'm a senior medical director at Takeda

Pharmaceuticals, and I'm the industry representative.

DR. WIDEMANN: Good morning. I'm Brigitte Widemann. I'm a pediatric oncologist at the NCI Pediatric Oncology Branch, and I have an interest in developing new therapies for children with refractory cancers.

DR. GOLDMAN: Stu Goldman. I'm a pediatric neuro-oncologist at Lurie Children's Hospital, formerly Children's Memorial in Chicago.

DR. SEIBEL: Nita Seibel. I'm a pediatric oncologist at the Clinical Investigations Branch of CTEP, NCI.

DR. ARMSTRONG: I'm Danny Armstrong. I'm a pediatric psychologist and executive vice chair of the Department of Pediatrics, University of Miami.

DR. WARREN: I'm Kathy Warren. I'm a pediatric neuro-oncologist from the National Cancer Institute, Pediatric Oncology Branch.

DR. SMITH: I am Malcolm Smith, a pediatric oncologist at the Cancer Therapy Evaluation Program, CTEP of NCI.

DR. BRIGGS: Caleb Briggs, designated federal officer, ODAC.

DR. SEKERES: Mikkael Sekeres, medical oncologist, Cleveland Clinic in Cleveland, Ohio.

DR. ZONES: I'm Jane Zones. I'm a medical sociologist, and I'm the consumer rep on ODAC, affiliated with breast cancer action and the National Women's Health Network.

MS. GOODMAN: I'm Nancy Goodman. I'm the patient advocate representative on the panel, representing Kids versus Cancer, which focuses on legislative and regulatory reform to accelerate pediatric cancer drug development.

DR. CASAK: I am Sandra Casak. I am a medical oncologist, and I'm in the Office Hematology and Oncology Drugs, FDA.

DR. REAMAN: Gregory Reaman, pediatric oncologist and associate director of the Office of Hematology and Oncology Products.

DR. YAO: Lynne Yao. I'm a pediatric nephrologist. I'm the associate director in the Office of New Drugs for the pediatric and maternal

health staff.

DR. SMITH: Okay. Very good. We'll begin.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that often members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of the meeting with the media until its conclusion. Also, the committee

is reminded to please refrain from discussing the meeting topic during breaks or lunch.

Thank you, and we'll now proceed with the FDA -- we'll now have the Conflict of Interest Statement from Caleb Briggs.

Conflict of Interest Statement

DR. BRIGGS: The Food and Drug Administration, FDA, is convening today's meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208, is being provided to participants in today's meeting

and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

During the morning session, there will be a presentation in general discussion of the potential applicability of pharmacological and cellular manipulation of the immune system as a potential therapeutic intervention in various pediatric cancers. The recent dramatic results of inhibition of the PD-1/PD-L1 axis and checkpoint inhibitors on normal T cells in melanoma and other adult cancers strongly suggest a potential role for such agents in the management of childhood cancer.

Information will be presented regarding pediatric development plans for two products that are in late-stage development for various adult oncology indications. The subcommittee will consider and discuss issues relating to the development of each product for potential pediatric use and provide guidance to facilitate the formulation of written requests for pediatric studies, if appropriate. The two products under consideration are, first, nivolumab, application submitted by Bristol-Myers Squibb Co., and second, MK-3475, application submitted by Merck Sharp and

Dohme.

This is a particular matters meeting during which specific matters related to Bristol-Myers Squibb's and Merck's products will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. Dr. Dunkel has been recused from participating in this session of the meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that Dr. Fingert is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Fingert's role at this meeting is to represent industry in general and not any particular company. Dr. Fingert is employed by Takeda.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. SMITH: Okay. Very good. We will now proceed with the FDA introductory remarks from Dr. Reaman. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Dr. Reaman?

Introductory Remarks – Gregory Reaman

DR. REAMAN: Thank you. On behalf of the agency, I'd like to again welcome the advisors to

this meeting and also thank both of the sponsors for their willingness to present and discuss to very exciting agents which have been already mentioned by Caleb Briggs.

This is a bit of an unusual and I think maybe perhaps groundbreaking event in that we have agents with very similar mechanisms of action. And we think that there is strong possibility that there is potential applicability of these drugs in the treatment of pediatric malignancies.

Recognizing the challenges that we have from the standpoint of small patient populations for study and recognizing the need for global drug development and international collaboration, I think the fact that we're seeing collaboration on the part of industry and regulatory agencies and the investigator community is really quite remarkable, and I think is noteworthy.

With that, we seek your advice in considering the planned pediatric development of these agents, information, and advice that will help us in the construction of written requests

that will go forward to advance pediatric development of both lambrolizumab and nivolumab in children. Thanks.

DR. SMITH: We will now proceed with a guest speaker presentation. That will be from Dr. Paul Sondel, a pediatric immunotherapy expert who will speak on this topic.

Guest Speaker Presentation - Paul Sondel

DR. SONDEL: Thank you very much, Dr. Smith. Thanks very much to all of you, and thanks also to Dr. Reaman, who specifically invited me to come and provide an overview regarding the niche and the rationale for the use of immunotherapy in the setting of pediatric oncology. As an introduction for this meeting, which is focused on the PD-1/PD-L1 access, Dr. Reaman suggested that I provide more of an overview of where cancer immunotherapy is actually going in the setting of pediatric oncology and some of the biological rationale for how it got there.

I have no conflicts to claim. And I want to start with some history. Really, the first

evidence that immune responses to cancer could make a difference in vivo came from mouse work published in the late 1950s, Richmond Prehn and Janet Main. They used a chemical carcinogen, methylcholanthrene, to induce fibrosarcomas in mice.

They could collect these fibrosarcomas, shown in this slide as tumor A1 or A2, and these could then be grafted into syngeneic mice. And because these mice were all genetically identical, they would grow. And they would grow and continue to grow, for example in that mouse on the left. And if nothing was done, the animal would die of that cancer.

But if the cancer was removed prior to it getting large enough to be lethal or to metastasize, the animal would survive that surgery. And at a later time, that animal could then be regrafted with some of that same tumor A1, and it would reject it. And this has been shown to be an immunological process that involves multiple components of the immune system, particularly

T cells.

If that same animal that had originally rejected tumor A1 is grafted with tumor A2, a separate methylcholanthrene-induced tumor in that same strain, that tumor would grow, indicating that there were separate transplantation antigens on these separate tumors even though they were induced by the same carcinogen in the same strain of mice.

Now over 50 years later, we know that those antigens are the results of mutations caused by these mutagens, which caused the cancers. And those different mutations, which occur spontaneously, are the cause of these transplantation antigens. So it raises the issue of how might the immune system be utilized to have an impact against cancer.

I want to acknowledge that I've gotten help in this talk with some slides that are provided by some experts, particularly in the PD-1 area. This slide is from Drew Pardoll of Johns Hopkins University. I've also gotten some slides from Mario Sznol from Yale University. But clearly, the

immune system has a capability to respond to a huge number of pathogens and to antigens. It has the weaponry to provide multiple different pathways of destruction of cells, and it has memory. And all of these could potentially be wielded against cancer.

So in the clinical arena, there are many opinions as to where the first evidence of immunotherapy was really proven to make a difference. But with respect to a physician-led intervention that has been clearly shown to work through immunotherapy, I think many would argue that the field of bone marrow transplant for malignancies, particularly leukemia, which began in the late 1960s, really has provided outstanding results for certain patients with very high-risk leukemias. And as shown by the International Bone Marrow Transplant Registry, looking at over 2,000 recipients of bone marrow transplants, the mechanism responsible for that beneficial antileukemic effect is an immunotherapeutic response.

These data just show that if you look at patients that have received a transplant, the ones that are most likely to relapse are the ones that have gotten a transplant from a twin or have gotten a T-depleted transplant. The ones that are least likely to relapse are the patients that have had some immune reaction, namely graft versus host disease. So the challenge of course is to identify what's causing the antitumor immunologic effect and somehow separate that from an anti-host tissue or GVH effect.

So in order to move this forward into clinical therapeutic manipulations, there are really two completely different forks in the road. One is to take a patient who has cancer, where we know that the patient's immune system has been interfered with by the cancer itself, and to use cells from a healthy donor as an immunotherapeutic in the setting of bone marrow transplant for some other allogeneic infusion. But in that setting, there needs to be a fair amount of cellular engineering and manipulation in order to avoid the

graft versus host kind of reactions against foreign major and minor histocompatibility antigens.

The other approach, and the one that has potentially much more greater applicability, is to use a patient's own immune system. But in that case, because the cancer has arisen in that patient and that patient's immune system is already impacted negatively by the presence of that cancer, there needs to be a fair amount of manipulation or activation of the immune system in order to have some beneficial effect against that cancer.

So in order to understand the interaction between the immune system and the cancer, Bob Schreiber from St. Louis has come up with this approach, looking at how an incipient cancer is interfacing with the host in which it is growing immune system. And this schema shows at the top the development of pre-neoplastic cells from normal tissues.

As those cells are changing and becoming neoplastic, they're expressing stress molecules or potentially modified proteins that might

potentially be antigens. They then interact with the immune system, and early on, the immune system is able to destroy those early cancers, and this is the elimination phase. But with time and selection in some individuals, some subclones of the cancer can survive. And as such, that residual cancer is dormant and is forming an equilibrium with the patient's immune system. And the two are coexisting. And then some time later in some patients, those dormant tumor cells are now selected in such a way that they are escaping from the immune system, and they grow and become clinically evident cancer.

So by the time cancer is diagnosed, all of these steps have undergone these interactions, and the cancer's that's identified clinically has already been selected for being relatively resistant to the patient's own physiologic immune interactions. Thus, when we're talking about immunotherapy, we're really not talking about physiological interactions of the immune system in cancer. We're talking about therapeutic or

pharmacologic, or supranormal manipulations, trying to get the immune system to do something that it wasn't able to do on its own.

There are many components of the immune system to consider as we're looking at the anticancer effect. The component that has had the most attention in research laboratories and in the clinic over the past 20 years is that of T-cell recognition, and we'll talk more about that later.

Next are the cells of the innate immune system: neutrophils, macrophages, natural killer cells. Next is the serological component to the immune system, namely antibodies. And in the clinical setting, the therapeutic component of this is that of monoclonal antibodies.

We need to be aware of how tumors themselves can suppress the immune system through a variety of pathways, including T regulatory cells, myeloid derived suppressor cells, and molecules released by the tumor to suppress the tumor in the microenvironment. And then we need to think about how these cells might be treated ex vivo and

infused into the patient.

Now putting this in the context of pediatric cancer therapy, we're in a somewhat fortunate position. And because of lab and clinical research, there's been a lot of progress in the treatment of childhood cancer over the past five decades. The majority of children will respond to their standard therapy of radiation, surgery, and chemotherapy. A majority of patients go into remission, and roughly 80 percent are cured, although with significant long-term side effects that are the result of those therapies, particularly the results of chemotherapy that are associated with mutations and other genetic damage.

The reason that children with cancer are still dying, for the most part, is not because they're not responding to their initial therapy. It's because the initial therapy is not good enough, and residual cancer then comes back and relapses and is resistant to those same therapies.

So with that background, what's the niche for immunotherapy in the setting of childhood

cancer? So unlike many -- not all but many -- adult cancers, where the initial therapy is not terribly effective, for children with cancer, the combination of surgery, radiation and chemotherapy is effective. And therefore, I think when we look at immunotherapy in the setting of children with cancer, we need to be looking at it in the setting of what are we already doing to have an impact on the child's cancer.

Because of these standard therapies that are being used, particularly chemotherapy and radiation therapy, can be quite immunosuppressive, many might argue that in order for these immunotherapeutic manipulations to have their best effect, they need to be timed in such a way to not have these standard therapies interfere with their efficacy.

So one approach would be to give the standard therapy, namely radiation, chemotherapy and surgery, to the patient. And then at a time that that patient is still at very high risk for relapse but has gotten whatever benefit one thinks one could get from such therapies, then to

integrate into that the immunotherapy approach.

In the setting of phase 1 and phase 2 testing, these patients have often been treated with multiple courses of therapies and identify patients that are appropriate for phase 1 or phase 2 treatment and test these approaches there. And then because there are different kinds of immunotherapies, one should look at what kind of cancer one is treating and how the particular therapy might have certain benefits for a particular disease.

So the overriding hypothesis for all of immunotherapy is that at least some immune cells have the capability of distinguishing somehow between normal and cancerous tissues. And this recognition could allow the selective recognition of cancers and destruction of cancer cells while causing little damage to normal tissues. The structures that T cells recognize on cancers are called antigens. The structures that the innate immune system recognizes on cancers are, in general, considered stress molecules or molecules

that label the cell as being unhappy or not normal.

In the setting of cancer antigens, there's a large list of different antigens that have been described in mouse tumors and in human cancers, multiple different categories. For the most part, the first five of these categories are molecules -- excuse me. The first four of these categories are molecules that are expressed highly on cancer cells but are also expressed on some normal cells, but hopefully on a very small population of normal cells or only on stem cells.

These are targets that would be expected to cause some degree of autoimmunity. By turning on an immune response against the cancer, one might expect some immune destruction of certain normal tissues. And one of the questions to raise is, is that autoimmune destruction going to be different in children than it is in adults, particularly if we're dealing with differentiation antigens that are expressed on earlier differentiating cells, might this be a problem particularly in very young children?

Second are cancer antigens that are unique to the cancer itself, the molecules associated with the mutations that are used to form the cancer itself. And some of these are shared between different cancers in different people, and some of these are unique to the individual cancer.

There are some antigens that are caused by viruses that cause cancer. Certainly, the HPV virus for example is a very important cancer antigen in cervical cancer, and vaccination against that is causing a benefit in preventing the cancer. But the focus of today's discussion is not prevention; it's on treatment. And there are very few cancers in children that are specifically caused by viruses.

Possibly, the most important antigens in cancer, at least based on animal research, are those mutations that are associated with amino acid changes in certain proteins that make those proteins immunogenic. And these occur sporadically as part of the genetic damage as part of the cancer itself.

Interestingly, if one looks at the spectrum of human cancer, the number of mutations that are found in each individual case of cancer differs dramatically between the different kinds of cancer types. On the right-hand side of this graph, you see the common cancers in adult: lung cancer, bladder cancer. At the very far right is melanoma.

These cancers have roughly two logs more mutations than the number of mutations that are seen in the pediatric cancers that are shown at the left. For example, neuroblastoma, the example that's starred, has roughly 14 non-silent mutations per case, non-silent meaning that there's a mutation in a protein that would potentially be immunogenic. It's about 20-fold fewer than that in melanoma. This might impact on how the patient's own immune system might be able to recognize pediatric cancers versus adult cancers.

So if we look at the components of an immune response to cancer, starting with the T cell response, the antigen-presenting cell, the APC, needs to see either the cancer or cancer antigens,

possibly given through a cancer vaccine. It modifies those molecules in a way to put them into the cleft of the MHC, the HLA molecule. And then the T cell has a receptor that recognizes the antigen as presented by the HLA. That is signal 1, and that's what's shown in the red box.

At that same time, a separate signal 1 is used to activate that T cell using a B7.1 or 2 molecule that interacts with a CD28 molecule on the T cell. If both of those signals occur at the same time in a T cell that has the capability to recognize that tumor antigen, that T cell is dramatically activated to proliferate, to release cytokines, to differentiate into either a helper or a killer T cell. And if that antigen is a cancer antigen, then those T cells would be able to recognize the cancer antigen and mediate an organized multi-potent immune response against this.

I'd now like to focus on three separate components of the immune response and how we might use them therapeutically in the setting of

pediatric cancer. Number 1 is T cell recognition; 2 is innate immunity, and 3 is antibody immunity.

In the setting of T cell recognition of cancer, here again there are really two forks in the road. The first fork is to say by the time the patient's diagnosed with cancer and we're interested in doing something immunotherapeutically for that patient, that patient's cancer has some antigens on it that the patient's own T cells are able to recognize. It's just that the patient's T cells are not potent enough to make an immunologic result against that cancer, and that patient's immune system needs some help. In other words, there's an immune response going on, but it's just not effective enough.

So there is a long list of things that are being used now in the clinic to try and expand the patient's own T cell response: expanding the specific population with vaccines; using molecules that can pan-activate cells that have been initially activated, like IL2 or IL-15; or using approaches to block the immunoregulatory

suppressive mechanisms; to purify and expand the patient's own T cells that are responding and give them back to the patient, the tumor-infiltrating lymphocyte approach; or to block inhibitory pathways, the checkpoint blockage approach that this morning's session is focused on.

But the other fork in the road assumes that by the time the cancer's been diagnosed, that patient's immune system just doesn't have what it takes to be able to recognize the cancer. And in that setting, there still are things one can do with T cell immunotherapy, but they involve taking cells out of the patient and modifying them genetically to give them the capability of recognizing the patient's own cancer and then making an immune response. This is the so-called chimeric antigens receptor T cell approach. Another is going to the use of somebody else's immune cells, allogeneic cells that have the capability of recognizing the patient's own tumor in the setting of bone marrow transplant or allogeneic infusions.

In the setting of the innate immune system, natural killer cells, macrophages, and neutrophils, again, there are a variety of agents that are being used in the clinic to activate these cells with the hope of having a beneficial antitumor effect. IL2 and IL-15 have been mentioned already. CD40 ligation uses a monoclonal antibody to activate macrophages in particular. GM-CSF and other toll-like receptor agonists can activate these innate immune cells to expand and recognize stress cells like tumor.

In addition, other approaches can try and block the tumor-induced immune suppression. One can select patients that have the appropriate kind of receptor genes to allow their innate immune cells to respond beneficially to their cancer -- I'll mention an example to this later -- or one can augment the immune cell to tumor cell ratio. This involves purifying the patient's own cells, expanding them ex vivo, like natural killer cells, and giving them back to the patient with other immunotherapies.

The last example, and the one that we'll focus the rest of this talk on, is that of monoclonal antibodies, which were first described in '75 and have now become amongst the largest selling drugs in the world for a variety of applications. In the setting of cancer therapy, there are two separate approaches for the use of monoclonal antibody.

One involves using monoclonal antibodies that recognize targets that aren't on the cancer cell at all. These antibodies recognize targets that are present on various immune cells or on other cells in the patient and are designed to have some beneficial effect against the cancer, such as monoclonal antibodies against endothelic [ph] growth factors that block the growth stimulation of cancer cells. The other category are the monoclonal antibodies that recognize antigens or molecules that are on the cancer cells, and these reagents have a direct effect against the cancer.

So the first category are those antibodies that see molecules not on the cancer but on normal

cells. I mentioned the example on the left of antivascular endothelial growth factor. On the right is an example of a checkpoint blockade antibody that has gotten a lot of attention over the past few years, ipilimumab. This is an antibody that recognizes an inhibitory molecule on T cells.

Shown in this cartoon is the activation of T cells through an antigen-presenting cell. The T cell sees signal 1 and signal 1, as I mentioned before, the antigens and a co-stimulatory signal. Once that happens, in order for a physiologic immune response not to get out of control, the T cell needs to be able to turn that response off so it up-regulates this molecule called CTLA4, which also recognizes B7.1. This activated T cell, when it sees that signal 2 has an inhibitory signal that turns that T cell off and prevents it from mediating further damage. By blocking that CTLA4 signal, one can keep that T cell responding.

So in the context of an immune response, where does CTLA4 versus PD-1 fit in? We talked

about this schema where an antigen-presenting cell is seeing a tumor antigen, presenting it through its MHC to the T cell receptor, and stimulating through signal 1 and signal 2. In that setting, the immune cell would be turned on.

However, in addition to that, if the CTLA4 molecule is up-regulated and gets its signal, there's an inhibitory signal that will prevent this immune activation from occurring. So if one blocks that CTLA4, one can enhance the likelihood of the immune response moving in that direction.

Now, once the immune system is turned on, it needs a way to turn itself off. And these immune cells, after they've been turned on and chronically stimulated, up-regulate a PD-1 molecule that allows them to see the ligand, PD-L1, that is expressed on some but not all tumors and some antigen-presenting cells. And that interaction will then turn these cells off.

So the PD-1 pathway involves recognition of the ligands, PD-L1 or PD-L2, on tumor cells or on certain antigen-presenting cells. That transmits

this negative signal that blocks the T cells' activation. In order to allow that T cell to continue being active, antibodies such as anti-PD-1 can block that receptor and prevent that inhibition, allowing a cell that's already been activated to continue on in its active function.

So clinically, over the past few years, there has been some exciting data with the use of anti-PD-1. I'll show a couple of examples that I've received from Mario Sznol documenting adult cancers, that single agent use of nivolumab is able to provide antitumor effects in adult cancers like non-small cell lung cancer, melanoma, renal cell cancer, with a significant number of complete responses and partial responses. Most interestingly, a number of patients that are responding are showing prolonged responses, indicating some kind of longer lasting immune effect even after the antibody therapy has been completed.

Again, looking at the different roles of CTLA4 versus PD-1, I'd like to focus on where these

interactions are likely taking place. The antigen-presenting cell that is turning on the T cell through signal 1 and signal 2 then would be activating through CTLA4 to turn the cell off. Blocking CTLA4 here will allow that cell to be activated. This happens early on in the T cell's response to the foreign antigen or to the cancer antigen and might be expected to happen in the lymph nodes and other central immune organs.

Once the CTLA4 has been blocked, that immune cell is going to be activated and circulate throughout the patient's body, and be able to go wherever it might see antigens that cross-react with it, and might be expected to cause some autoimmune reactions.

In contrast, the PD-1 arm takes cells that have already been activated through that signal 1 and signal 2 and have already trafficked to the tissues, where they are recognizing the antigen that is keeping them stimulated. And in that setting, the interaction of PD-1 and PD-L1 might turn those cells off in the tissues. Blocking PD-1

might allow those cells to continue having their function. In order to have this effect, one would expect that these cells that express PD-L1 have to have been activated already.

So based on that hypothesis, in order to turn on more cells that are going to be augmented by PD-1 blockade, it makes sense to use a combination approach. And this exciting work involves a combination of anti-CTLA4 and anti-PD-1. These data are data presented at ASCO by Jen Wolchok. And as you can see, using this combination approach, the majority of patients with melanoma that got this combined therapy showed very striking antitumor effects with quite prolonged responses. The prolonged response involved a significant long-term stability for so many patients long after the therapy had been completed

Now, in order for the PD-1 antibody to work, one would expect that you have to block the PD-1 molecule from seeing its ligand, PD-L1. And so there's some nice data suggesting that the efficacy of PD-1 antibody in the clinical setting may

correlate with the expression of the PD-L1 molecule on tumors, as shown here. But the interaction of the PD-1 receptor and PD-L1, requiring PD-L1 on the tumor can allow a T-cell that's responding against a tumor to actually cause the tumor to start to change.

So a PD-L1 deficient tumor, a tumor that's not expressing that ligand, can actually up-regulate it in response to immune damage or other damage. And that may potentially explain why, with that adoptive approach, the combination of anti-CTLA4 and anti-PD-1 was able to get significant responses even in patients that were PD-L1 negative, likely by up-regulating PD-L1 in the tumor.

So looking at this in terms of moving forward, one might expect that for patients that have a strong endogenous, antitumor response going on from their own immune cells already, that ongoing immune response is trying to destroy the tumor, which is up-regulating PD-L1 on the tumor. And in that setting, blocking PD-1 should help

those responding cells to do an even better job.

In contrast, if a patient does not have a very strong immune response against the tumor already going on, and if their tumor does not express PD-L1, in that setting, it may make sense to use some other kind of therapy to try and destroy tumor and/or turn on an immune response to allow up-regulation of PD-L1 on the remaining tumor. And in that setting, one could then use anti-PD-1 antibody and get a beneficial response.

I'd like to switch now to a very brief overview of monoclonal antibody therapy separate from the use of antibodies that recognize targets on normal tissues, namely the whole use of monoclonal antibodies against antigens that are present on cancer cells.

These antibodies are able to recognize tumors, and they can be conjugated with a variety of toxins or other molecules to carry them to tumors. They can also mediate specific immune function, destruction against the tumor. There are a variety of separate monoclonal-based agents that

have been used: single-chain antibodies, amino toxins, conjugates, and chimeric antigen receptors. Bifunctional antibodies such as blinatumomab utilize this approach and allow an antibody recognition structure to recognize the tumor, and then bind to a T cell and turn on the immune response.

So I'd like to now focus on there separate places where an antibody binding to the tumor, interacting with an effector cell, such as a natural killer cell, might potentially allow an immune response to be augmented therapeutically. Each of these six separate places are where molecular interventions can try and benefit this interaction therapeutically.

I'd like to focus on the activation state of the immune cells on what's happening at the FC under the antibody and on other receptors that can impact the interaction between the immune cells and the cancer in the fact of a monoclonal antibody.

This is a situation for a neuroblastoma. Patients with high-risk neuroblastoma as of a few

years ago, diagnosed with metastatic disease, have on the order of a 30 percent disease-free survival. We began working with Ralph Reisfeld who generated an antibody against the GD2 molecule. That work was done in parallel to work by Nai-Kong Cheung, who generated a separate antibody against the same antigen. This molecule is expressed on neuroblastoma, melanoma, and certain other pediatric sarcomas, as well as some adult sarcomas; but not on most epithelial cancers or normal tissues.

Dr. Jackie Hank in our laboratory did some in vitro experiments that in summary showed we could get much better antitumor effects if we treated neuroblastoma cells with the antibody and activated the immune cells with IL2 at the same time. However, when we took blood from cancer patients, we couldn't get a very strong reaction from some patients. We had very little reaction from other patients.

These patients happened to be adults that were referred to our team to get IL2. After

getting a few weeks of in vivo IL2, we took blood from those same individuals and now could see striking killing of the neuroblastoma cells in vitro, as long as we had both the IL2 and the antibody in the in vitro reaction.

We hypothesized that we could generate those same kinds of conditions in patients with cancer by giving them this same mini-week regimen of IL2 along with the monoclonal antibody when we knew their innate immune cells were activated. We worked with my colleague, Mark Albertini, to treat melanoma patients. And we worked through the children's cancer group and then the Children's Oncology Group to generate phase 1 and phase 2 data in neuroblastoma. We learned a lot about pharmacodynamics and pharmacokinetics. But for the most part, patients with bulky tumors weren't showing much response.

We then teamed up with Dr. Alice Yu from UCSD. She, along with Dr. Cheung at Sloan-Kettering, had been using GM-CSF to activate some innate immune cells, namely neutrophils and

macrophages. We were using IL2 to activate the natural killer cells. We also knew that if we were to use this approach in patients with very small amounts of disease rather than bulky disease, we might get better penetration of the antibody, and we wouldn't have to contend as much with the myeloid derived suppressor cells or T regulatory cells that might suppress the immune system.

We generate a regimen that was tolerated acceptably by children that were in remission after an autologous bone marrow transplant. I won't go through the details. Then in 2001, we began moving this towards a phase 3 study through the Children's Oncology Group that began accruing patients in 2003. Accrual ended in 2009. Children had finished all of their surgery, radiation, or autologous transplant, and chemotherapy, and were then randomized to that immunotherapy regimen or not, along with cis-retinoic acid.

We learned that the immunotherapy arm was providing benefit as far as event-free survival. At the two-year time point, the significant

differences were 66 percent versus 46 percent. And at that point, we stopped doing the standard therapy, and all children were moved over to the immunotherapy arm.

So that's an example of activating the effector cells with IL2 and GM-CSF and using a monoclonal antibody together. The last example I'll give involves a molecule that fuses those concepts. This is a humanized antibody that recognizes that same GD2 antigen. This was created by Steve Gillies and Ralph Reisfeld. And it acts to activate cells through their FC receptor. But in addition, IL2 is put on to the end of each immunoglobulin heavy chain to activate cells that have IL2 receptors.

In mouse models, this molecule is quite potent. What's shown here are mice with metastatic neuroblastoma that got treated with saline. Each of these bars is the number of metastases in the liver. These mice got treated with antibody and IL2, and these mice got treated with antibody linked to IL2, using the same molar amounts of the

two agents, as shown in the middle graph.

Based on this, we initiated clinical trials of this fusion protein. We also did mouse work to ask when is the best time to use this kind of therapy. What's shown here are the number of metastases in mice with metastatic neuroblastoma. These mice got treated with saline. These other groups of mice all got treated with the exact same immunotherapy regimen, 5 days of this antibody liked to IL2. The only difference is when we started the therapy.

You can see that the earlier we start the therapy, after the tumor is put in, we see a far greater effect, consistent with our hypothesis that this approach is going to work better in minimal residual disease for a variety of reasons.

Why is linking IL2 to the antibody more effective? We've done a fair amount of preclinical data on this. I'll skip the data, but just show our conclusion. When antibodies are mediating antibody-dependent cellular cytotoxicity, they work through the FC receptor on effector cells, like

natural killer cells or macrophages that are binding through the antibody to the tumor, and allowing recognition, and activation, and killing.

When we use an antibody that has IL2 on the end as well, we can get some additional activation through IL2 receptors that might augment the activation through FC receptors. And finally, there are a variety of cells in the immune system that don't have FC receptors but do have IL2 receptors, and these cells can bind to the tumor through the IL2 that is now coating the tumor using this antibody IL2 fusion protein.

So we've done clinical trials. A phase 2 clinical trial of this approach looked at the difference of patients with neuroblastoma, refractory relapse neuroblastoma, that was either bulky and measurable by an MIBG scan -- excuse me -- bulky and measurable by a standard CT scan or MRI. That's stratum 1; or patients that had relapse disease but had less bulky disease. Couldn't be seen by a CRT or an MRI but could be seen by MIBG or bone marrow histology.

In this phase 2 study, which has been published, 7 out of these patients showed some clinical benefit. All of the patients that showed clinical benefit were in stratum 2, the ones with the less bulky disease. None of the patients with bulky disease showed response. We did the T test and came up with a p-value of .03 between the two separate arms, consistent with our mouse data, saying that this kind of approach is better if there's less bulky tumor.

The last point I'd like to make is looking at other receptors on the effector cells and how they can be used to influence the efficacy of immunotherapy. Here are natural killer cells, and they have a variety of receptors. One set of receptors are called killer inhibitory receptors or killer immunoglobulin like receptors, KIR. It's the red receptors shown on the NK cell at the top. These receptors recognize HLA molecules, and they transmit an inhibitory signal. This is an oversimplification, but the KIR molecules that have been focused on most are the ones that transmit the

inhibitory signal.

If the NK cell has that receptor, but it does not recognize the HLA molecule that triggers it, the inhibitory signal won't be activated. And as a result, that NK cell can be turned on and kill the target.

These interactions have been proven to be of great importance in bone marrow transplants for both acute myeloid leukemia and lymphocytic leukemia in children and adults. But in addition, they seem to be important in autologous bone marrow transplants. And this is because the KIR genes are controlled by chromosome 19, while the HLA genes are controlled by chromosome 6.

As such, each of us has a repertoire of our KIR genes and a separate repertoire of our HLA genes. Roughly, 60 percent of the population has inherited at least one KIR gene for which we don't have an HLA gene. Such patients are called mismatched, and their NK cells might be expected to be a little bit more active or twitchy. Forty percent of the population has inherited a

repertoire of KIR genes for which every KIR gene has a corresponding HLA gene. That 40 percent might be expected to have NK cells that are slightly less potent. When you look at the results of autologous transplant for pediatric childhood tumors work coming out of St. Jude and Sloan-Kettering, those children with the mismatched situation do better.

We hypothesized that this KIR/KIR/ligand and mismatch really didn't pertain to bone marrow transplant, but pertained to immunotherapy that acted through natural killer cells like ADCC. So when we looked at our patients that got treated with the antibody and linked to IL2, all seven of those patients that showed benefit were in the KIR mismatched group. None of them were in the KIR matched group, really statistically significant and showing that it is the natural killer cells that seem to be responsible for this effect and that other receptors on the effector cells may be important.

Since we published that result, the

Sloan-Kettering team has done a much larger study through the labs of Kathy Hsu and Nai-Kong Cheung, looking at patients with neuroblastoma, treated with an anti-G2 antibody either without or with a bone marrow transplant. And in all cases, there's a clear association of antitumor benefit with this KIR mismatch setting.

So in summary, there is a lot that can be done with monoclonal antibodies. They have an effect against childhood cancer. This slide really summarizes where in vivo ADCC might be going, including the use of antibodies and effector cell activating agents, using the KIR/KIR/ligand and other receptor benefit in order to try and have an effect with the important caveat. And in order for this to apply, we need to identify better targets on pediatric cancers that might be recognized by monoclonal antibodies.

So in summary, there are several agents that are already being used immunotherapeutically. They have impact on cancer and are already approved. Some of these agents are already being used in

children and in adults with efficacy, such as rituximab and others. Many of the agents that could be applied in children have efficacy in adults.

The setting of using these approaches in children may be somewhat different than adults because we have therapies that are already curing many children and putting so many into remission. So we need to build our immunotherapy strategies around that success and integrate it into them.

Finally, we might need to look at how we can add these immunotherapies to our standard therapy currently, and then do very careful clinical work to see how, in the future, we might be able to use immunotherapy to get some efficacy, and then gradually pull back on some of the genotoxic chemotherapy that's causing long-term effects in our children, to see if immunotherapy might be able to substitute for some of that.

So I'll end there and just recognize many of the people that have been involved in our research that I've tried to mention along the way. Thanks

very much.

(Applause.)

Clarifying Questions from Subcommittee

DR. SMITH: Thank you for that excellent introduction to the session, Paul. We have time for some questions from the committee on the presentation.

UNIDENTIFIED FEMALE: So I'm not an immunologist, so this may be an ignorant question. But whenever we see the cartoons of the immune cells and tumor cells, there's one T cell for each tumor cell. And I know that's an oversimplification, but is there a minimum number of T cells that you need or that function in order to get a response to the tumor cells?

DR. SONDEL: It's a great question. At the single cell level, the cartoons are accurate. A single T cell interacting with a single tumor, if it's the right kind of T cell with the right receptor and right activation state, is able to kill that single tumor. Now, that right T cell is a more quantitative question because if you look at

the number of T cells you've got in your body, it's only a tiny, tiny fraction of them that have the right receptor for any particular antigen, even strong antigens like viral antigens.

So the fraction of T cells that might have the right receptor for a tumor antigen might be on the order of 1 out of a thousand or less. So in order for this to happen in vivo, that T cell has to get to the tumor.

At the quantitative level, if a T cell has the right kind of receptor and the right activation mechanism, it can be stimulated to expand and proliferate an increase in its numbers. So some recent work using the chimeric antigen receptor T cell approach has been able to show by counting the number of T cells given to the patient and estimating the amount of leukemia cells in the patient, that a single T cell with the right receptor given to a patient with leukemia can induce a complete response that requires that that one T cell must have killed a thousand separate leukemia cells. Now, it didn't do it by having

that one T cell kill all the leukemia. That one T cell went through several rounds of division and expanded in the patient. But that one T cell's progeny were able to kill all those leukemia.

DR. SEKERES: Thank you, Dr. Smith.

So you mentioned there are potential issues with immunotherapy in children, including differentiation antigen may see developing tissues in an infant, limited non-essential tissues in an infant. It's unclear whether developing tissues express antigens shared with cancers. Immune attack may interfere with normal growth, et cetera.

Have you seen any of these clinically or are these all theoretical? So in the examples of when immunotherapy may have been used in kids already.

DR. SONDEL: I raise those really as theoretical examples. Some of these antigens that are expressed on adult cancers are expressed on certain differentiating cells. But at this point, to my knowledge, there has not been a really systematic evaluation of the expression of these antigens on pediatric cancers and particularly on

early developing pediatric tissues. Such an approach needs to be done.

In the setting of patients with refractory or relapse cancers that are going to be dying, it seems appropriate to test some of these approaches that are showing benefit in adults and to look carefully at the possibility of some of these toxicities in children. We need to be aware of it, but I think some additional lab work needs to be done both preclinically and careful monitoring of children that are going to be getting these treatments.

DR. SEKERES: But just to be clear, you're talking about lab work. This has not been seen clinically in kids before.

DR. SONDEL: Correct.

DR. SEKERES: Okay. Thank you.

UNIDENTIFIED MALE: A couple of questions. One, could you comment on what is known about the frequency of tumor-infiltrating lymphocytes in different childhood cancers and can be evidence for some preexisting reactivity of T cells? And the

second question, you showed the hypothesis that the immunotherapy may be effective in cancers with more mutations, like melanoma, lung cancer. Pediatric cancers might be less likely to respond to immunotherapy because of fewer mutations per cancer cell. What are the data to support that?

So those are the two questions.

DR. SONDEL: Again, the data are somewhat sparse. A lot of the data are these laboratory data looking at the number of mutations, and mouse data, where these phenomena has been looked at. In general, not always, careful studies done in evaluation of immune system interacting with mouse tumors have been predictive of what we've seen when these concepts are applied to the clinical setting if they've been applied in a way that fairly extrapolates from the setting in the mouse to that in the patients.

With respect to tumor-infiltrating lymphocytes, there are a number of pediatric cancers where there are some tumor-infiltrating lymphocytes, but it's not an across the board for a

particular histology. Clearly, within a particular histology, some patients might have more tumor-infiltrating lymphocytes than others, as is seen in the adult setting. And some of this is being regulated by some of the host genes that influence the way the immune cells function, as well as the sporadic antigens expressed on the tumor. So here again, I don't think that there's a lot of data.

With respect to fewer antigens potentially on pediatric cancers, that was referring to these sporadic antigens associated with genetic damage that are causing amino acid substitutions that in theory might look foreign to the immune system because they reflect proteins that have been modified as different from what's on the patients' own cells that would be causing tolerance.

Separate from that though, these differentiation antigens that our immune systems are potentially tolerant to, but tolerance can be broken. There's no reason to suspect that there's any difference in the number of those on pediatric

cancers than there are on adult cancers.

Some preliminary data looking at adults with melanoma suggests that some of the immune responses in patients that are getting checkpoint blockade are actually directed against some of those differentiation type antigens, like marked or tyrosinase that don't require a mutation in order to recognized. And so one would expect those same kinds of mutations to be seen on pediatric tumors.

DR. SMITH: Are there any other questions? Dr. Reaman?

DR. REAMAN: Paul, can you just comment. In the pediatric tumor situation with the lower frequency of mutations and the resulting decreased immunogenecity of tumor antigens, if they're present, is there a way to attempt to overcome that with stimulation with IL2 and GM-CSF? Is that a potential approach?

DR. SONDEL: Yes. So if in fact those mutated antigens are the most important -- although in response to Malcolm's question, they're not the only ones. But if those are very important,

anything we can do to try and boost the patients' immune response to expand the rare population of T cells that have the kind of T cell receptor rearrangement to recognize those should potentially enhance the ability to do that.

So even though there's only 14 separate actionable mutations in a case of neuroblastoma, it seems to me that there's a pretty reasonable chance that at least one of those mutations is going to involve an amino acid substitution that could presented by an MHC in order to turn on a T cell response. It's just getting that rare T cell that's got the capability of recognizing it to expand. But again, remember the third slide I showed from Drew Pardoll, the T cell receptor capability repertoire has the potential to generate T cell receptors that could recognize 10 to the 18th antigen.

So we should have the capability to see the vast majority of mutations, even if rare, by our T cells. The question really is how immunogenic are those individual mutations.

DR. REAMAN: And then the other question is, given that pediatric oncology, at least the approach to childhood cancer, has been multi-agent and multimodal, is there a potential for multiple immunotherapeutic approaches? So ADCC and checkpoint blockade, is that something that has some potential hypothetical basis or consideration?

DR. SONDEL: We're very excited about that, and we're fortunate to be just initiating some laboratory studies, trying to test that. But since some NK cells do express PD-1, it would make sense to try and induce ADCC and combine that with PD-1 blockade. That's just one example. But just as the incorporation of chemotherapy in childhood cancers has really shown that you need to attack cancer from many different angles in order to prevent escape, when one's using the immune system, it makes sense to have separate antigens that are being targeted as well as separate pathways of destruction.

Therefore, using T cells and using ADCC and activating innate cells like macrophages, using

them against different antigens, all of this I think makes a lot of sense. And the question is how do we best put them together and learn in our clinical studies what's working.

DR. SMITH: Thank you very much again for that great introduction.

We will now proceed with an industry presentation from Merck, Sharpe and Dohme. But before we do so, I have to read a statement.

Both the FDA and public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it's important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the

outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the presentation from Merck.

Industry Presentation - Robert Iannone

DR. IANNONE: Good morning. I'd like to start by thanking the FDA for this opportunity to present the pediatric plans for MK-3475 on behalf of Merck. By way of introduction, I'm a pediatric oncologist by training. Prior to joining Merck, nearly nine years ago, I was on the faculty and staff of the University of Pennsylvania and Children's Hospital of Philadelphia in the section of bone marrow transplantation.

After giving some background on MK-3475, I'd like to discuss our strategy for identifying

pediatric indications, present our preliminary pediatric development plans, and conclude with a discussion of challenges and developing anti-PD-1 therapies in childhood cancer.

This slide shows some of the key development milestones for MK-3475, starting with the melanoma IND application not quite three year ago. Melanoma orphan drug designation was granted in November of 2012 and breakthrough designation in January of 2013. There has been a pediatric waiver for melanoma in place since April of 2013, and one was granted for non-small cell lung cancer in October of 2013. Our pediatric investigation plan procedure is underway in the European Union.

MK-3475 is a high affinity, high potency humanized IgG4, PD-1 blocking antibody. It is engineered to have a mouse variable region, which is specific to PD-1 grafted onto a human framework. It has high affinity with a KD in the 29 picomolar range and high potency with an IC50 of 600 picomolar. Consistent with an IgG4 antibody, there has been no observed cytotoxicity thus far.

MK-3475 is formulated for IV administration. Dosing in adults is weight based, and the current formulation will support weight-based dosing in the pediatric population all age subsets.

This slide summarizes the clinical pharmacology of MK-3475 in adults. It has approximately a 4-week half life. It's exposure increases linearly at and above 0.1 mgs per kg, one given every 3 weeks. And there's been a very low occurrence of anti-drug antibodies with no observed impact on PK.

Results from 135 patients with advanced melanoma treated as part of Protocol 1 was recently published in the New England Journal of Medicine. Patients in this cohort received 10 mgs per kg every 2 weeks or 2 or 10 mgs per kg given every 3 weeks. The confirmed response rate per RECIST 1.1 was 38 percent. There were 38 partial responses and 6 complete responses. Forty-eight of these patients had been previously treated with ipilimumab, and response rates were similar between the groups.

This waterfall plot shows on the Y axis the percent change from baseline in the sum of longest diameters of target lesions and patients across the X axis. Seventy-seven percent of patients had reduction in their tumor burden. And as you can see from the color coding, responses were similar between patients who previously received ipilimumab treatment and those who were naive. This swimmer plot shows time to response and duration of response with individual patients plotted on the Y axis and time in weeks on the X axis.

The median duration of response had not been reached at the time of this analysis, with 11 months of follow-up. And 42 of the 52 patients had been continuing treatment again at the time of the analysis. There were 10 discontinuations, and 5 of these were due to toxicity. Interestingly, two patients who had discontinued therapy, pictured toward the bottom of the swimmer's plot, had an improved response even after discontinuation.

While drug related AEs were common, grade 3 to 4 AEs occurred in 12.6 percent of patients.

Most commonly, these were fatigue, rash, pruritis, diarrhea, myalgia, headache, nausea, and asthenia. There were no treatment related deaths in this cohort.

This slide describes the potentially immune related AEs. Six patients had grade 1 to 2 pneumonitis. Eleven patients had hypothyroidism, and one of these was grade 3. There was one case of grade 3 hyperthyroidism, and this was associated with grade 2, adrenal insufficiency.

Two patients had grade 3 or 4 transaminase elevations, and 2 patients had grade 3 renal insufficiency. One of these patients was documented to have nephritis on renal biopsy. We observed vitiligo in 12 patients, and there was one death in a 96-year-old man in the setting of pneumonitis due to complications from bronchoscopy and pulmonary biopsy. It's worth noting that colitis has been observed outside of this particular cohort of patients. Most treatment related AEs were successfully managed with treatment interruption and treatment with

glucocorticoids.

Results also from Protocol 1 in 38 patients with non-small cell lung cancer were recently presented at the 15th World Conference on Lung Cancer. These patients had received at least two prior therapies and were given MK-3475 at 10 mgs per kg every 3 weeks. The confirmed and non-confirmed response rate per RECIST 1.1 was 21 percent, and the median duration of response had not yet been reached at 62 weeks.

Interestingly, preliminary data suggests that higher levels of PD-L1 on the patients' tumor were associated with increased clinical activity. Responses were observed in 4 out of 7 patients with higher PD-L1 expression and 2 out of 22 patients with lower expression. Drug related AEs occurred in 53 percent of patients, and only one was grade 3 to 5. The overall profile of the adverse experiences were similar to the melanoma experience with rash, pruritis, fatigue, diarrhea, arthralgia, back pain, cough, and decreased appetite being the most common.

There was one instance of each of the following AEs, which were of interest: hyperthyroidism, hypothyroidism, pneumonitis, and pulmonary edema, which was the only grade 3 case. And this on further inspection was likely to be a case of pneumonitis, and that it responded to corticosteroids. And there was no evidence of congestive heart failure. There were no treatment related deaths in this cohort.

I'd like to now shift to a discussion of our strategy for identifying pediatric indications for treatment of MK-3475. This figure by Melera et al. published in Clinical Cancer Research shows that PD-1 expressed on T cells can interact with PD-L1 on tumor cells. And PD-L1 and PD-L2 on tumor associated macrophages. We know that by blocking both ligands PD-L1 and PD-L2 with MK-3475, we can see dramatic antitumor responses.

Having also observed a relationship between PD-L1 expression on tumor and clinical outcomes with MK-3475 treatment, our hypothesis is that pediatric tumors that express PD-L1 are more likely

to respond to MK-3475. Therefore, our strategy for identifying pediatric indications is two-pronged.

We'll explore pediatric banked tumor and genomic databases for evidence of PD-1 pathway up-regulation. And then we'll use this information to prioritize tumors for evaluation in our phase 2 study. Because we know that there would be some limitations to that approach, we also want to include an adapted design in phase 2 that would allow us to treat and explore multiple other indications. And then we would expand any indication where we observed clinical activity.

I'd like to now discuss in greater detail our preliminary pediatric development plans, which are currently under discussion as part of the PIP procedure in the European Union.

Phase 1 will include children between 6 months and 18 years of age with advanced melanoma, advanced relapsed/refractory solid tumors, and lymphoma. We expect to evaluate 2 or 3 dose levels using a typical 3-plus-3 dose design, but also to include an expansion cohort to confirm

the safety of the anticipated recommended phase 2 dose. Our starting dose would be no more than 50 percent of the exposure in adults at the maximum administered dose, and we would use data from the ongoing study to determine how many additional dose levels should be evaluated and what those dose levels should be.

Accordingly, the phase 1 objectives are to define the dose limiting toxicities, the maximum tolerated dose, and the maximum administered dose to characterize the PK in order to select a single dose that best approximates the PK exposure in adults at the recommended phase 2 dose that would then be used for further development in phase 2. We would also assess preliminary efficacy, again, to inform potential indications in phase 2.

Phase 2 will be a single-arm safety and efficacy evaluation at the pediatric recommended phase 2 dose in children between 6 months and 18 years of age. Again, tumor types will be prioritized based on the PD-L1 expression data, as well as from signals observed in phase 1.

Additional indications will be evaluated as part of an adaptive design. For example, we'll enroll an initial cohort of around patients, evaluate for clinical efficacy, and then potentially expand that indication up to 20 to 25 patients to look for clinical efficacy.

The objectives for phase 2 would be to assess the safety and tolerability at the pediatric recommended phase 2 dose to evaluate objective tumor responses according to standard criteria and also to assess the relationship between PD-L1 expression and clinical efficacy.

Our current proposal to meet global pediatric regulatory requirements is to select one pediatric indication based on phase 2 results for further evaluation in a randomized comparison to standard of care. The details of this phase 3 study design, such as eligibility, comparator, and primary endpoint, will depend on the indication selected. We'd be very interested in the committee's input on whether a single-arm efficacy study could provide definitive evidence of efficacy

in any one particular clinical context.

I'd now like to discuss briefly our strategy to use PD-L1 as a biomarker for patient enrichment. Merck has developed an immunohistochemistry assay based on a mouse monoclonal antibody capable of detecting PD-L1 in formal and fixed parafin-embedded human tumor samples. Preliminary data from MK-3475 clinical trials support its continued investigation as a predictive biomarker. If PD-L1 is truly predictive, then enrichment would help avoid treating patients who might not benefit from the drug.

This table describes how we plan to use this assay in clinical development. In phase 1, we would use this on an exploratory basis and only retrospectively. And phase 2 as part of the adaptive indication finding study, we would enrich patients on the basis of PD-L1 expression in their tumor in order to increase the likelihood of identifying a clinical signal on that particular indication. How we would use this in phase 3 really depends on what we observe in phase 1 and

phase 2. But certainly this could be his prospectively either to enrich patients or to stratify to ensure balance across arms.

We've already covered several of the potential challenges in developing anti-PD-1 therapies and MK-3475 in childhood cancers. I'd like to now spend some time on the question of combination therapies and the risk/benefit in children.

With regard to combination therapies, I would first emphasize that anti-PD-1 monotherapy could well be the optimal approach for some indications in some clinical settings. The optimal standard of care combination will certainly depend on which indications show monotherapy efficacy with MK-3475. And we should be aware that some combinations may actually have the potential for antagonism if the combination partner is immunosuppressive, as was mentioned previously. Certainly, the timing and the sequencing of the combinations will be important, especially if there is a component of immunosuppression from the

combination partner.

We think that immunotherapy combinations are very promising and are likely to be very important. Many of these combinations are currently under evaluation in adults, and we'll learn much from the outcome of those studies.

We were asked to consider the potential impact of the developing immune system on efficacy with anti-PD-1 therapies. While there are clear differences in immune function when comparing young children to adults, MK-3475 has the potential to be efficacious in pediatric tumors as well. Even young children are capable of mounting an immune response to either vaccines or viral infections. Therefore, we hypothesize that if a tumor has an endogenous antitumor immune response and has up-regulated PD-L1, then there's the potential for those tumors to respond to MK-3475.

We were also asked to consider the potential for adverse effects of long-term immune checkpoint inhibition. As you know, cancer immunotherapies have the potential to result in immune related AEs.

These immune-related AEs are being characterized with anti-PD-1 therapies in adults in terms of their organ site predilection, manifestations, kinetics of onset, and the optimal management. We should be aware that manifestations in children may certainly differ across age subsets. And therefore, careful monitoring and physician education will be critical.

Certainly, ongoing pediatric trials with other related immune therapies may highlight potential differences in the AE profiles between adults and children, which could help inform monitoring strategies in the clinic. And we look forward to a discussion from the committee on how to optimally monitor and protect the safety of children in these trials.

In summary, Merck is committed to the development of MK-3475 in childhood cancers. Pediatric development is ongoing, but it is in the early stages. And we believe we'll be further informed by some of the preclinical studies that we had mentioned and also the ongoing trials in

adults. We believe that evaluation of PD-L1 can be very important for identifying pediatric indications, but also potentially to enrich or stratify in clinical trials.

As mentioned, our PIP procedure is ongoing in the European Union, but the plans that we presented today were really intended to address the requirements in both the U.S. and Europe. We truly believe if well aligned, we'll facilitate pediatric development. Thank you very much for your attention.

Clarifying Questions from Subcommittee

DR. SMITH: Thank you. We can now have questions from the committee. Dr. Widemann?

DR. WIDEMANN: I was wondering if you saw in the trials that you did a relationship between PD-L1 expression and adverse events, and then between adverse events and responses observed. And finally, between adverse events and age, if you have looked at that?

DR. IANNONE: So for the first one, I don't know that we've looked at the data in a way that we

could link PD-L1 expression to adverse events. With regard to the other questions you asked, in the non-randomized data that we published in the New England Journal, it appeared that efficacy and adverse events were higher in the highest dose group. Again, those were non-randomized data, and we're in the process of evaluating in randomized cohorts the potential effective dose on both efficacy and safety.

DR. SMITH: Dr. Seibel?

DR. SEIBEL: On slide 9, you showed the swimmer's plot, and it showed that around 10 weeks is when you saw PRs. During that time, did some tumors grow? You also mentioned that two patients had improved responses after discontinuation. How long after discontinuation? So how long would you have to monitor these patients for responses to make sure they haven't had a response?

DR. IANNONE: Sure. With regard to the first part of your question, our first scheduled assessment wasn't until 12 weeks, so there's a bit of a bias in terms of might there have been a

response observed even earlier or might you have observed first an increase and then a tumor response. So that's still being characterized, and we have some opportunities in other trials to better understand that, certain tumors that are easier to visualize, for example.

Certainly, for melanoma patients who had skin lesions, we're seeing responses even earlier than 12 weeks. We have seen patients who initially show progression to then ultimately have a response. That's not necessarily common, but it has been observed. And we have observed that in order to accurately assess the response rate, it does take some time. So many patients will go from, say, a stable disease even at 12 weeks or beyond to showing a first objective response after that period of time.

DR. SEIBEL: And then how long for the two that discontinued?

DR. IANNONE: They're shown on the bottom, so you can see where the bar ends -- sorry, can't use a pointer, but you can see where the bar ends.

And then you can see in blue and red the documentation. So just a few weeks afterwards.

DR. SMITH: Ms. Goodman. We have several other questions lined up. If you would keep your mic on when you talk and off when you're not talking.

MS. GOODMAN: Thank you. A two-part question. First of all, what input have you had to date from European or American pediatric clinical oncologists in the design of this plan? And my second question is related to your parallel process with the EMA towards the PIP.

To the extent that this process results in different recommendations or requests with respect to trial design or to the extent that pediatric oncologists who in fact execute these trials request modifications, are you willing to undertake additional studies or additional work, or are you willing to request that these recommendations be implemented in your PIP through amendments or through your current negotiations?

DR. IANNONE: So to start with the second

question, we're very willing to consider input from multiple sources and to accommodate that in our pediatric development plans. I believe that the most optimal approach would be to have strong alignment between our commitments in Europe and in the U.S. And that will ultimately facilitate the fastest, most efficient development in pediatrics. So that's what we're striving for, and I think this morning is a great opportunity to achieve that.

With regard to the first question, we've had many, many conversations with key opinion leaders in Europe and the U.S. specifically around the content of the ongoing PIP proposal, but in addition just more broadly around how can we understand which pediatric indications are going to be most likely to respond. And that's a separate -- what I describe in this presentation as a workstream that's already ongoing.

DR. SEIBEL: If I could just do a follow-up just so I can clarify. But if there were new recommendations that came out of this process, would you be willing to go back to the EMA and

ensure that they are incorporated in your PIP or undertake them in some other capacity?

DR. IANNONE: Out of this process here today?

DR. SEIBEL: Yes.

DR. IANNONE: Yes. And we have that opportunity given where things stand.

DR. SMITH: Dr. Warren?

DR. WARREN: Just as a follow-up to the pseudoprogression question earlier, your adverse events listed are primarily generalized adverse events. Did you see any local reactions in the tumors at all? I mean, part of the concern here is for potential CNS indications, and we would see an increase in tumor size so to speak.

DR. IANNONE: So we're working very hard to get paired tumor biopsies pre- and post-treatment. And we have some clinical trials where it would be easier to do that so that we can specifically look at some of the factors ongoing in tumors. That's not always so easy. So for the most part, what we have to rely on is imaging of the tumors to look at

size, for example.

As I mentioned before, while I wouldn't call it common, there are some cases where an initial increase in tumor size probably represents an inflammatory response and not necessarily growth of that tumor. And over time, we then observe that that tumor has an objective response.

DR. WARREN: So just in follow-up, did you see any local erythema or pain around where the tumor was or a more focal response?

DR. IANNONE: In the case of melanoma, that's skin based. Many patients will have some skin-based disease as well as visceral disease. You can see the tumor changing and generally shrinking. You may see it become more red, for example, initially.

DR. SMITH: Dr. Sekeres?

DR. SEKERES: Sure. Thank you, Dr. Smith.

A couple of questions for you, and I'm not sure if the first one is more appropriate for you or for Dr. Sondel. I had always been under the impression that as kids develop from infancy, the

immune system matures. For example, you don't see -- well, you may see some, but you don't see as much seasonal allergies in infants because their IgEs haven't matured yet.

So how do we know that these approaches will work the same in a child who's 6 months, which is the lower age of what your enrollment is, and 18 years?

DR. IANNONE: Sure. As we've been thinking about this question, we're really separating potential for efficacy from the potential for adverse events. In terms of the potential for efficacy, it's clear that kids have a robust enough immune system, even early on, to handle viral infections and to give robust responses to vaccines. So we think the important thing there is what's happening in the tumor, which is why we've emphasized so much the importance of screening tumors for evidence of preexisting immune response. And up-regulation of PD-L1 is evidence that the PD-1 pathway is abrogating that immune response.

I think where you observe that in pediatric

tumors, the chance of having a response with MK-3475 is high. That's a little separate than to say, our children who have different stages of, say, thymic function, would they be more or less susceptible potentially to adverse effects? That's unknown.

I think that as we begin to do studies with other related immune therapies, we'll learn whether the profiles look similar or different in adults, and that will really help us do the appropriate monitoring.

DR. SEKERES: So just thinking about response -- and thank you for dividing into adverse events versus response. I think that's a nice division. If we're just thinking about response, I wonder if Dr. Sondel would be able to comment on whether you think that a 6-month old would have the same immune response to allow efficacy as someone who's 18 years old?

DR. SONDEL: While an infant of 6 months might not have quite as developed an immune response as someone who is 18 years, an infant of

6 months has a very well developed immune system and has a repertoire of T cell receptor recognition that is huge. It's able to recognize the subtle differences in different vaccine subtypes and show with specificity, at both the T cell level and the antibody level, elegant specificity of the immune response.

So I would think by a few months of age, the immune system's capability to recognize subtle antigenic differences could be there. Although the number of T cells that would respond to it may be small, the whole purpose is to expand that subpopulation, and that's what this immunoregulatory approach is designed to do. I think it would be different if we were talking about a neonate.

DR. SEKERES: Okay. That's really helpful. Thank you.

The second part of my question is, you've described a pediatric melanoma population, patients who have tumor types prioritized based on PD-L1 expression data. Do you have any -- we haven't

seen any presentation on the epidemiology of these diseases in kids. What kind of population are you looking at for melanoma and for non-melanomatous tumor types that express PD-L1?

DR. IANNONE: So the key strategy for this pediatric development plan is really not to focus on melanoma, but to focus more on identifying pediatric tumors that would benefit. And the reason is that we believe that the biology of melanoma in adults and mostly adolescents, right, because it's even rarer in young children, is very similar. Responses to conventional therapies are similar between adults and adolescents. And we have every reason to believe that those children, adolescents with melanoma, will respond as well. So it's much more heavily focused on other indications.

DR. SEKERES: So I'm sorry. I don't think that quite answered the question.

DR. IANNONE: So the second part of the question was, are there epidemiology to understand for other indications what the PD-L1 expression is

like. And in the literature, as far as I can tell, there's not very much. So we're in the process of undertaking staining banked tumor tissues ourselves and tying that to the clinical outcomes; for example, understanding the prevalence, the prognosis, et cetera, across pediatric indications. And there are many places where that can be done, and we're in the process of sorting that out.

DR. SEKERES: So we don't have a lot to hang our hat on here. So can you tell us there are -- what's the epidemiology of melanoma in kids? Are all of those melanomas PD-L1 susceptible? What other tumor types have you seen any PD-L1 expression to justify the inclusion criteria?

DR. IANNONE: So we're very early in the process of this work, and so we really have no data to share on the epidemiology of PD-L1 expression across pediatric tumors. I don't think it will differ in melanoma, which is why I'm much more focused on other indications. So we don't know what yet to expect, but we think that's an important place to start.

DR. SMITH: Dr. Armstrong?

DR. ARMSTRONG: Thank you. A couple of questions. In your AES, was cognitive function, acute cognitive function, assessed at all in the AEs?

DR. IANNONE: Assessed through usual physical examination and patient interaction, but not specifically with cognitive testing.

DR. ARMSTRONG: The reason for asking the question is we know that cognitive late effects are a big issue for children. And those are not assessed in adults, and we're seeing executive function processes, speed, attention problems. I didn't know if those were assessed or not.

DR. IANNONE: Not in a formal way. And what I'd say is what we know from pediatric oncology experiences, that's very often tied to, say, brain radiation for leukemia, or high-dose methotrexate, or intrathecal methotrexate. There's nothing about this mechanism that would make me worry, but I think you make a good point, that developing children, we need to pay attention to that.

DR. ARMSTRONG: Well, inflammatory processes in sickle cell disease and HIV are actually being linked to cognitive function, so it's something to consider.

The second question I had is that Dr. Sondel pointed out a neuroblastoma and also in the leukemias the importance of tumor burden. And with the melanomas, was there an attempt to get to minimal residual disease, or at the point of using the drug, was this just the tumor as is with a biopsy?

DR. IANNONE: Our melanoma experience is a mixed of patients who were relapsed and refractory, so at later stage, but also even first-line therapy. I think the fundamental problem in melanoma, unlike many pediatric tumors, it's not very responsive to conventional therapies. So most patients had a considerable amount of disease.

Despite that, we're clearly seeing dramatic responses. And you could see from the swimmer's plot that in some cases, you see an initial partial response. And then after some period of time, a

complete response even with bulky disease.

DR. SMITH: Dr. Fingert?

DR. FINGERT: As I'm looking at the agenda, I see we have five complicated questions to go through, starting -- and we only have one hour to do it later on at 10:45. So I would like to get to what I think I'm projecting is an important question for the sponsor. As I look at their presentation, slide 16 and following, they've really gone to efforts to lay out for us the details of their immediate current plan, a phase 1 plan, including their goal to escalate to an MTD. It's not just a bridging study to like the adult MTD that some people do with phase 1's.

The conclusion, he later spoke about how they have an interest in monitoring and protecting the children. So I'd really like to ask if we could discuss at some time -- and I don't see that there's any other time -- without naming a particular drug. Are there experiences about clinical activity of immunotherapies that we could bring to help comment on this plan.

I mean, I see that they really laid it out in some detail -- multiple slides about each stage -- and the elements of their protocol. And I think people at this table have more experience with different types of similar immunotherapies, again, without naming them, that might be relevant to -- especially with their goal of managing risks and enrolling children in this kind of a trial design.

DR. SMITH: Would you like to comment in terms of the rationale for your proposed designs?

DR. IANNONE: In terms of safety monitoring? Our rationale is to do everything that we know how to carefully monitor children in these studies. But I think a key element of this is that there will be emerging data from ongoing related immunotherapies where this will give us a lot of insight into whether we should expect something different in children or not. And if we observe that, that will help us. Otherwise, we have a lot to go on in the adult experience in terms of how to monitor, how to do a diagnostic evaluation to

really understand the nature of the toxicity, then how to withhold treatment, intervene with therapeutic intervention such as glucocorticoids, et cetera.

DR. FINGERT: To give an example that comes to my mind, are you planning -- or do other members of this group feel it's important to be more cautious than you would be with, grafting an adult trial into pediatrics, about things like screening for opportunistic infections and C. diff. in kids that roll in from -- these are kids that would have seen a lot of antibiotics from other institutions and rolling in.

With CTLA4 targeted therapies, I am aware there have been some very severe and life threatening and fatal colitis events that in retrospect were possibly associated with the fact that the kids also had -- or the adults also had C. diff. In the Crohn's population, I'm aware that safety's been a problem with other things. Like listeria has been fatal and CMV colitis. Things like that have been problems in developing those

drugs in the pediatric population.

So anticipating that, not necessarily excluding the kids, but doing the right kind of cultures may be of interest. But again, I'm not a pediatric oncologist, so I'm sort of putting that to the table so that we can get to advice as how they can succeed with their phase 1 program.

DR. SMITH: Okay. And we can come back to that in the discussion period.

Dr. Reaman? I had two questions, but first wanted to respond Ms. Goodman's question about the progress with the pediatric investigation plan at the EMA and its similarity, if you will, or concordance with what we might do here as far as a written request. And we do have a process through the Office of Pediatric Therapeutics, where we actually provide common commentary, if you will, on sponsors' plans.

Although the PIP and the written request may not be identical, they're not opposed to each other. And we're not asking the sponsor to do one thing in one development plan and not in another.

So they may be somewhat parallel, generally complementary. We have experience now doing this with a number of agents, and these are agents that both the agency and the EMA want to make sure that there is global agreement in our approach, recognizing that it has to be an international development program and there are limited numbers of patients. And the only way that this is going to work is if we worth together.

But Rob, I wanted to just get a little bit more clarification on the recommended phase 2 dose-finding strategy utilizing the exposure data in adults. But it looks like you're using three different dose and schedule strategies in adults. So do you plan to select one of those, all three of those, and carry them into children, or what is the plan?

DR. IANNONE: So we have ongoing randomized evaluations of dose and schedule that will clearly inform our starting dose strategy. And once we know that, it will give us a couple of options. So if we're at a higher dose for example, in the

adults, then we might start at 50 percent of the maximum exposure, which would clearly put us in an active range based on the adult data we have even now. And then we would have the opportunity to escalate from there, which is why we say we may need two or three doses.

If it turns out we're at a lower dose in adults based on those randomized evaluations, then we certainly could start with a dose that targets that specific exposure in adults and still be at an exposure that is several-fold lower than the exposures that we have at the max administered dose in adults. So we want to build in some flexibility there in terms of how to initiate the dosing.

DR. FINGERT: Thanks. And then the other question, is there any correlation or has there been any correlation with the development of adverse events and exposure, duration of exposure to MK-3475? Or did some of these occur early or is there no relationship at all?

DR. IANNONE: So maybe you could take that two ways. One is overall exposure and then

duration of effect. In terms of the overall exposure, the data that we published show that both efficacy and adverse events are higher in the highest exposure group. But again, those are non-randomized data, and we're weighting a randomized comparison.

What we observed across all dose groups is that AEs do accumulate somewhat gradually. It eventually plateaus. For example, if you were to look at just the first month, you certainly wouldn't capture a majority of them.

DR. SMITH: Okay. Dr. Goldman, and then Dr. Seibel. And I have a couple of questions, and then we need to finish this session and head to the break.

DR. GOLDMAN: In your phase 2 design, you note that the tumor types will be prioritized based on the PD-L1 expression from banked tumors. But I heard you earlier say you have no data on any of these pediatric tumors at this time?

DR. IANNONE: Not at this time. We're obviously very early in our planning, and we're

actively seeking sources not only of banked tumor tissue to stain with our in vitro diagnostic for PD-L1 expression, but also to look into genomic databases to get some sense of how pediatric indications might rank order for things like PD-L1 expression. We think that we'll have those data certainly in time for the initiation of phase 2, and we think that will be important to consider.

DR. SEIBEL: Could you comment on patients who had CNS lesions with melanoma and if they responded?

DR. IANNONE: As part of the eligibility criteria for most of the studies, patients who had CNS disease are eligible only if they were adequately treated. We did have a few cases of even in that setting seeing tumor regressions. And Dr. Rubin has some insight also into those cases.

DR. RUBIN: I'm a medical oncologist, and I'm involved in the development. And I just wanted to make sure that you had information from me as well. So that's correct. Patients had to have stable, previously-treated brain lesions to be

eligible. And those who were eligible, we did see responses in those patients. I don't think we can specifically say what happened with the brain lesions, however. We don't have that data at this time.

DR. SMITH: A couple of questions. Relating to the PD-L1 expression, could you comment on how you set your cut points for the level of expression and frequency of expression; how uniform expression is across the tumor? So if you just have a small piece of tumor, how representative that would necessarily be of a larger tumor or metastatic disease, whether there's stability and uniformity of expression. And then, if your PD-L1 expression levels are low, how that effects your development plans in pediatrics.

DR. IANNONE: So it's clearly a work in progress. And some of the things that you mentioned around the potential for sampling error or the patterns of expression that might differ across indications are clearly going to be important factors. Despite some of that

complexity, as was shown in the introductory - presentation, there clearly seems to be a relationship. I showed you some of our own data. So we think, given what we know about the biology and what we're observing, even with the methods that we have in hand, that it's important.

Then I would just point out that for the purpose of identifying indications, those considerations are a little different than they would be for the purpose of enriching a patient in the clinical trial. So what I'm describing around looking at banked tumor tissue and genomic databases is really to try to do a rank ordering to understand which tumor sort of fall in that group that are above average for a PD-1 pathway elevation versus those that are at the bottom of the list.

That's an initial cut. Again, that's not going to give us the final answer, which is why our phase 2 design is intended to be flexible and adaptive to the data that we observe.

DR. SMITH: But your phase 2 design is built on PD-L1 expression, and that being basically a

criteria for entry?

DR. IANNONE: So in the adapted design, we think that by enriching for PD-L1 we can increase the probability of identifying a clinical signal, based on the data that we would observe. In that setting where we might have limited data for those specific pediatric indications, we would probably take a very simple approach, such as excluding only those patients in whom you have really no evidence of PD-1 pathway upper regulation, no evidence of PD-staining on any biopsy that they have, whether that be archived or new.

Dr. Rubin may have more to add to that.

DR. RUBIN: I would agree. I just would note that we have looked at different histologies, including melanoma in lung, and we do think the assay, looking for expression of PD-L1, we'll be capable of doing that across multiple different histologies using our antibody.

DR. SMITH: Given that heterogeneity and expression could be significant, and you'll get one, perhaps a small biopsy, what's the level of

activity, based on a small biopsy, when the biopsy is negative and treatment proceeds?

DR. IANNONE: The empiric data that are emerging count for those kinds of challenges in doing this. And so despite those challenges, we still think the data are important and showing a relationship between what you can find in that setting and clinical outcomes.

Again though, the approach would be that -- and this was true of the published vapor out of Hopkins where if a patient had five biopsies and only one was positive, then they were counted as positive, for example. If a patient has all their archive specimens that are available negative, and they have a new biopsy that shows that it's positive, you might consider that positive. And when you calibrate it that way, it emphasizes the negative predictive value instead of the positive predictive value.

DR. RUBIN: Malcolm, I might add to that I think it's important also to separate the development plan from individual patient decisions.

So we're focusing on -- we think it will expedite finding the most active places for use in pediatrics. But that doesn't mean that if we get a positive result, we wouldn't go back and study efficacy in a PD-L1 negative population.

DR. SMITH: And final question, could you comment on the up-regulation operating characteristics of your phase 2 design that has basically a first stage of 5 patients and presumably stop if no responses are observed?

DR. IANNONE: The sample size that I put on the slide is really an example being in the range of 5. And the idea is that even with 5, especially in the setting of enriching for PD-L1, gives us reasonable power to detect a signal. And I would point out that while we would define this with conventional criteria such as RECIST objective responses, we'd want to look at other factors as well, such as maybe prolonged stable disease and tumor change, tumor shrinkage, on a continuous scale to be sure we're not missing a signal in what's a relatively small sample set.

Once we expand to 20 or 25, if we're really in a refractory population, it's pretty good power to distinguish from a fairly low response rate of 5 or 10 percent.

DR. SMITH: We have Dr. Reaman.

DR. REAMAN: I commend the plan to look at possibly enriching the population, but I just want to make sure that the biopsies, the retroactive biopsies, are diagnostic biopsies, not biopsies that are obtained immediately before going on any sort of investigational therapy, number one.

Number two, if you find that there is variable expression across a number of different diseases, would your development plan change somewhat so that rather than looking at a specific histologic tumor indication in the pediatric setting, you would just look at those tumors irrespective of histology, where there's evidence of PD-1/PD-L1 access activation?

DR. IANNONE: So starting with the second question, most definitely we would adapt to data. Our whole objective is to be flexible enough to

adapt the data, preclinically as well from the ongoing studies.

So for example, if we find that neuroblastoma, based on genomic analysis or banked tumor tissue, is high in PD-L1 expression, then we could go right to a larger sample size in that phase 2 that might be 20 or 25 patients. But we wouldn't want to just do that. Just because we didn't see anything in Wilms, we wouldn't want to exclude those patients.

So Wilms might be good for the adaptive part, where we look at a few. And if we see something, especially in a patient who's particular tumor is up-regulating PD-L1, that might tell us that, well, PD-L1 regulation is not necessarily common in Wilms, but when it occurs, patients respond. And that would be useful information, and then we could expand from there.

Then in terms of your first question, if a patient has an archival specimen that shows up-regulation in PD-L1, I don't think the biology suggests that any intervening treatment would

really cause that to not be the case. If they have an endogenous antitumor immune response, there would be no reason to insist on another baseline biopsy.

If the reverse is true, if they have in all their archived specimens no evidence of PD-L1, it is quite possible that an intervening therapy had triggered an immune response. And that immune response was in fact abrogated by the up-regulation of PD-L1. So a patient could opt to have a biopsy. And if that were positive, I would say that that's justification for enrollment.

DR. REAMAN: I guess I'm just asking because of what we heard earlier about the lack of -- or the relative lack of the mutations, resulting in immunogenic antigens in pediatric tumors. Many of these are going to be diagnosed relatively early in a patient's course, and that might be the archival specimen that said develop. So does an anti-PD-L1 response or a PDL-response develop later, and is that something that could possibly be missed in the diagnostic specimens.

DR. IANNONE: Right. I also would like to comment on the issue of frequency of mutation. It's I think a very good hypothesis that mutation frequency could be increasing the odds that you'll have a cancer new antigen that the immune system is responding to. In fact, we have a trial open at Hopkins, where we're looking at patients who have micro satellite instability, and therefore a high frequency of mutations. So I think it's a very important hypothesis.

On the other hand, it's also possible that the nature of the mutation and the type of tumor antigen is important, even if there aren't many mutations in a particular patient. And I think of the CML example that was highlighted earlier, where CML is exquisitely responsive to allotransplant. And it probably has to do with the nature of the antigens that are derived from that particular translocation.

DR. SMITH: Okay. Thank you. We need to proceed to the break now. We'll shorten the break, take a 10-minute break. Committee members, please

remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any members of the audience. And we'll resume at 10:05. Thank you.

(Whereupon, a recess was taken.)

DR. SMITH: We will now proceed with the industry presentation from Bristol-Myers Squibb. And again we have a statement. And the music stopped, so that's good.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor,

including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you do not choose to address the issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking. And we'll proceed now with the BMS presentation.

Industry Presentation - Mark Moyer

MR. MOYER: Good morning. My name is Mark Moyer. I'm a global head of regulatory sciences for Bristol-Myers Squibb. And on behalf of Bristol-Myers Squibb, I'd like to thank the committee for providing us feedback on our proposal today and also for the Food and Drug Administration for inviting us today to make this presentation on our proposal for what we hope will be an efficient and effective pediatric development plan, in initiating that.

After my brief introductions, I'll have

Dr. Renzo Canetta, who's our global head of clinical research for oncology for Bristol-Myers Squibb, present our proposals, along with the data that supports nivolumab pediatric development and plan as we're proposing it.

Our goal is to develop a global pediatric program which efficiently and also safely evaluated nivolumab in tumors that are relevant in the proposed population, not just those that we're studying in adult, but those that have unmet medical need in the pediatric patients. We've had multiple collaborations that have led to an innovative proposal. This included in March submission of a pediatric investigational plan in Europe's submission as well as a pediatric study plan that was submitted to the FDA at the same time that were a duplicate of each other.

We had a meeting in July of this year with both FDA and the National Cancer Institute in order to bring together a collective wisdom regarding our proposal, which has led to today's presentation as to the proposal we're making. We had a

teleconference with the Pediatric Development Committee of EMEA in September, and we've had multiple collaborations and consultations with U.S. and European pediatric experts.

As a snapshot on this slide, to the left there are three elements of innovation that we're proposing. The first, as we would like to initiate, our phase 1 portion at the adult dose. There will be two cohorts of 2 to 11 years old and also 2 to 18 years old. And we would enable dose de-escalation as needed.

That would move to expansion cohorts in which we are proposing to include young adults. We would look at four tumor types specifically that have been proposed by our experts, both in the U.S. and Europe, and we would look at additional tumors based on emerging data from tumor banks as far as biomarker, as well as adult data that would indicate we should be moving forward in other tumors.

In parallel to that, we would like to move then into our first combination therapy, which is

with nivolumab and ipilimumab in combination, and we'd be looking at that, gain, into two cohorts in order to evaluate the safety of the combination. But we'd be looking at that in a dose escalation format, starting at 1 milligram per kg of nivolumab and ipilimumab, and then moving to 1 and 3 of the two compounds, as we had this on a Q3 week basis.

Right now I'd like to present Dr. Renzo Canetta who will go through the details of the proposal as well as the data that supports that.

Industry Presentation - Renzo Canetta

DR. CANETTA: Thank you, Mark.

The compound we are presenting to you today is a checkpoint inhibitor as for other agents in the class. That's not a target directly to tumor cells, but it targets the immune system to the PD-1 receptor located on the T lymphocytes. This targeting blocks the interaction of the T cell with two different ligands, PD-L1 and PD-L2. This results in an activation of the immune system to recognize and attack the tumor. Mind you, this compound is fully human IgG4 monoclonal antibody.

In the current experience of nivolumab in adult patients, there has been no clear-cut evidence of a dose response relationship in terms of safety, and this was up to the dosage of 10 milligram per kilogram and across multiple different tumor types. The regimen of 3 milligram per kilogram every 2 weeks was chosen for the ongoing large phase 3 program in multiple tumor types going on in adults. And this actually constitutes the largest experience that we have accumulated with this agent in adults.

The exposure in pediatric patients is expected to be similar to that of adults receiving the same dosage on a milligram per kilogram basis. The clearance of nivolumab decreases with the decrease of body weight.

We have consulted with pediatric study investigators, and they supported the initiation of the pediatric program at the dosaging schedules chosen. We've also been consulted [indiscernible] by the experience with ipilimumab in pediatric patients, and this data supports a similar safety

profile for this type of checkpoint inhibition as in the case of adult patients.

We have conducted a fairly large phase 1 trial with nivolumab in more than 250 adult patients, and this slide represents selected adverse events. There are some key observations that could be made.

First of all, over the range of dosage started, there was no consistent to dose effect in terms of safety, as you can see across the board and for the totality of the data. Second, the incidence of a severe grade 3 and 4 adverse event was fairly low for this type of pathology, for this type of population.

Third, the type of adverse events that we have observed were consistent with what has been seen with other checkpoint inhibitors with the exception of pneumonitis. Early in the course of the development program with this agent, there were actually three deaths related to pneumonitis that occurred in this trial.

Of note, the safety profile that is depicted

here covers a fairly long period of observation, as patients were kept on treatment up to progression or for a minimum of 2 years of treatment.

We can say that the same observation for lack of a dose effect can be applied to the efficacy of nivolumab. Here you see the slide representing response data as assessed by standard RECIST criteria. In addition, there was a small number of patients that presented delayed responses according to what was observed in other checkpoint inhibitor trials. But these patients were not contained in the numerator of this slide.

Considering this is a very heavily pretreated group of patients, 47 percent of these patients had received 3 or more prior regimens for the treatment of their metastatic tumors. We believe that these are relevant results in their expressing tumor shrinkage, and the absurd activity was seen in different tumor types, including tumor types that historically or traditionally have not been considered to be immunogenic. This observation may be important also for the pediatric

pathology.

These objective responses, as you have seen earlier, have the tendency to be very durable and have the tendency to result in very long median survival.

The second aspect of our proposal consists of the introduction of expansion cohorts. After consultation with investigators, we will initiate the evaluation in these selected cohorts of pediatric tumors that present a certain unmet medical need. There is the possibility to add additional cohorts, and this is going to be based upon signals that we can detect from the clinical program that I will allude to later, from the adult program, and also from what we observed in the early phases of the study.

Another aspect that we want to introduce in this program is to allow the inclusion of young adults to the expansion cohorts. This is a raising issue in today's cancer reality in this country and elsewhere. A factor that could influence the selection of these additional cohorts and

prioritize them is the presence of the PD-L1 receptor ligand on pediatric tumors. I think it's fair here to provide at least three caveats.

Caveat number 1, the results at the present in the literature have been obtained with different assays using different monoclonal antibodies and testing actually different tumors, primary or biopsies from metastasis. Second and even more importantly, the cutoff that has been utilized to determine positivity of these assays are different across different laboratories. And third and perhaps even more important, we have seen meaningful objective responses in patients whose tumors were PD-L1 negative. So that's something that needs to be kept in mind.

We have developed together with Dako a standardized assay that we plan to utilize in evaluating from tumor banked pediatric tumors, and we are planning to utilize this both with U.S. and European investigators. This is the same assay that we will apply, and it is part of all of our phase 3 programs for monotherapy of nivolumab and

also for the combination of nivolumab and ipilimumab. And this is part of our prospective retrospective analysis plan for these phase 3 trials.

The third aspect of our proposal involves the possibility to start the study in the combination of immunotherapies and checkpoint inhibitors. Indeed as you have seen early this morning, in the lymph node and in lymphopoiesis organs, the T cell priming occurs to interact with mature antigen presenting cells that express MHC and other costimulatory ligands, including B7.

The inhibition of the CTLA4 by ipilimumab enhances T cell activation and proliferation of tumor-specific T cells that traffic then to the tumor site. In the tumor microenvironment on the right part of this slide, peripheral tolerance of tumor-specific T cell is induced and maintained by the part for your PD-1 and PDL ligands preventing tumor-specific T cell from reacting against the tumor cell. And blocking this pathway with an anti-PD-1 antibody restores the T cell function,

allowing for T cell mediated tumor elimination.

Ipilimumab actually today represents the current totality of the existing experience with checkpoint inhibitors in pediatric patients. The pediatric branch of the National Cancer Institute is conducting a phase 1 trial of this agent in this population. And these are the data that are preliminary and have been so far made public. As you can see at the time of the publication, 26 patients were accrued, age 2 to 21 years old, and the majority with a diagnosis of melanoma or various types of sarcoma.

In this relatively still small number of patients, at low dosages of ipilimumab of 1 or 3 milligram per kilogram, the incidence and the severity of immune related adverse events appear to be low. However, with increasing dosages, 5 and 10 milligram per kilogram, there was an increase in incidence and increase of severity of these adverse events. And the nature of these adverse events did not really seem to differ from our experience in adult patients.

In this trial at a time of public report, there were 7 patients that had the stable disease for a duration of 4 months or more, including a single child with melanoma that received 14 courses of ipilimumab in excess of a treatment of more than one year and is still continuing on treatment after 14 months.

The combination of ipilimumab and nivolumab is supported by preclinical models. Even more importantly, the initial clinical results obtained in adult patients with melanoma has contributed to generate remarkable interest. And as you can see, these are the data, shown even earlier today, presented by Dr. Wolchok at ASCO this year.

This particular panel refers to the dosage and schedule, 1 milligram per kilogram of nivolumab and 3 milligram per kilogram of ipilimumab, that has been brought further into the phase 3 clinical program that we're running right now. This combination is given every 3 weeks for 4 dosages of concomitant ipilimumab and nivolumab, and then there is maintenance that continues with nivolumab

alone every 2 weeks at 3 milligram.

Now, as presented by Wolchok and collaborators, these results are quite promising. Mind you, from the earlier presentation of this morning, these results have been obtained irrespective of PD-L1 expression, so similar efficacy has been seen in both cohorts of patients. And of note, these responses have also been very durable and resulting in 80 percent one year survival, as presented by Sondel.

Now, this slide is not a comprehensive list of adverse events, but it focuses on those events that are most relevant for today's discussion. And here you have depicted the monotherapy nivolumab experience on the right, the ipilimumab monotherapy experience as in the package insert of the drug, and the early experience with the combination. Obviously, there are limitations in comparing across trials and across the series. And also there is the limitation that the combination series is still quite limited, with only 53 patients.

However, as you can see, the combination

seems to provide for an increase of toxicity as compared to the two monotherapies. Note however that the no safety events have been identified that are different from what has been reported for the various experiences in monotherapy with a potential exception of mostly asymptomatic increases in lipase and amylase.

Thus, back to our proposed initial pediatric study design, we feel confident that we can start with nivolumab monotherapy at the dosage and schedule that currently has been utilized in adults. We feel confident that because of that, we can move rapidly to the expansion cohorts in patients that have tumor types that are relevant to the pediatric pathology; whereas, we're not necessarily interested in tumor types that may exist only in adults, those resulting in regulatory waivers, and waivers, and waivers. We have interest in including young adults with a relevant pathology and relevant diagnosis.

Accordingly, we are also very interested in expanding our knowledge on checkpoint inhibitors by

studying their combination also in pediatric pathology. The portion of the study on the right part of the slide will adopt a more traditional dose escalation approach given the limitation of the existing adult experience. So we will start at 1 milligram per kilogram of each component and then escalate to 1 milligram of nivolumab and 3 milligrams of ipilimumab, which is the current utilized dosage and regimen every 3 weeks for the adults. Here again, we plan to study separately the two cohorts of patients according to age.

Now there are additional components for our pediatric development plan; first of all, the known clinical biomarker study by which we have interrogated tumor banked samples utilizing our standardized assay for PD-L1 expression. As part of the pediatric investigational plan in consultation with the European health authorities, we are planning a modeling and simulation study. And finally, of course, we will move to confirmatory efficacy study for the appropriate signal defined in the expansion of the cohorts.

In summary, I think that we have the goal to efficiently develop a global pediatric program for nivolumab in tumors that are relevant to pediatric patients. We believe that we're introducing innovative approaches, and these are needed to accelerate pediatric development. We are strongly convinced that the immune oncology agents provide today fairly unique opportunities for collaborative pediatric development plans, both with health authorities and investigators alike globally. Thank you for your attention.

Clarifying Questions from Subcommittee

DR. SMITH: We're open now for -- do you have final comments?

MR. MOYER: No. We're open for questions.

DR. SMITH: Okay. We're open for questions then from the committee.

UNIDENTIFIED FEMALE: I'm wondering if you could provide a little bit more information on how the diagnosis for the expansion cohorts were selected.

MR. MOYER: These were based on

consultations, both in the U.S. and Europe, as to what the investigators believed were relevant tumors that had high, unmet medical needs, but was not based on any tumor marker information.

DR. SMITH: Could you comment on the data that would support the ipilimumab plus nivolumab combination overcoming the negative prognostic significance of absent PD-L1 expression?

MR. MOYER: Certainly. I'd ask -- Renzo Canetta, could you discuss that? I think it was presented also in Dr. Sondel's presentation a little bit.

DR. CANETTA: Again, I believe that when it comes to the biomarker, the caveats that I have alluded to apply both to the monotherapy and to the combination. Certainly, the data that Dr. Sondel has shared with us today and to be presented by Dr. Wolchok indicate that maybe there is the possibility to overcome the type of negativity by the combination of the two agents.

I think that we shouldn't forget also what Dr. Sondel alluded to earlier and that we also

alluded to in our presentation, that there is a function of priming by cytokines that can be factored in. And here again, think about the fact that we are dealing with sometimes archived material coming from initial diagnostic biopsies or surgical specimen. And then we're dealing with patients that with time might have developed metastases or different location of tumor.

Again, there is a factor of heterogeneity that is important; the fact that we are planning in our adult program to interrogate the heterogeneity by taking different biopsies from the same tumor and asking whether the expression is equal in all the biopsies.

DR. SMITH: Dr. Reaman?

DR. REAMAN: A couple of questions. Could you just elaborate a little bit more on the pneumonitis? Is it a clinical diagnosis of pneumonitis? Do you have histopathologic --

MR. MOYER: I'd ask Dr. Dana Walker from our pharmacovigilance group to comment on the safety and the pneumonitis that was observed.

Dr. Walker?

DR. WALKER: Dana Walker, global pharmacovigilance. In reference to your question, the pneumonitis diagnoses are both clinical and histopathological in some cases. There are clinical symptoms of dyspnea and hypoxia, in some cases, that correlate with radiologic changes on X-ray and/or CT scans. Additionally, we've had bronchoscopies and lung biopsies performed on several of the patients that have shown inflammatory changes in lymphocyte infiltration.

DR. REAMAN: And I think it was like how many patients that actually had the pneumonitis? I mean, I guess I'm concerned about the lymphoid infiltration. Was that consistent in all of the patients that had bronchoscopies or biopsies, or in some patients? And can you talk a little bit about whether the lymphoid infiltrate was further characterized subset analysis?

DR. WALKER: Sure. Inflammatory changes were fairly consistent in the biopsies. I can't speak necessarily to the lymphocyte subset analysis

on the biopsies.

DR. REAMAN: Just another question. The plan for the combination study, or what you're doing now in adults with the combination of the two agents, and just nivolumab as maintenance, can you just explain the rationale for the selection of nivolumab for longer duration of therapy rather than ipilimumab rather than continuing the combination if you see increased responses with the two agents together?

MR. MOYER: I'll ask Dr. Fouad Namouni, who's the head of our global development for nivolumab to address that specific question, being part of this whole program. It's his design.

MR. NAMOUNI: For pneumonia global development, Bristol-Myers Squibb. In our initial observation of the combination of the two agents in melanoma, most of the activity, as you have seen on that spirogram presented, happened within the first 12 weeks or even earlier. And ipilimumab is administered every 3 weeks; for 4 doses [indiscernible] every 12 weeks. We did not clearly

see an additional role that ipilimumab can play in the maintenance phase. However, monotherapy, nivolumab can continue that activity over time.

DR. SMITH: Dr. Warren?

DR. WARREN: So a basic question I think is, do we know the effects of steroids on the mechanism of action? The patients who are on steroids prior to enrolling, do they have any effect whatsoever, and can that be investigated prior to the study --

MR. MOYER: Your question is patients that have steroids prior to the initiation of therapy, and then also those that started --

DR. WARREN: Right.

MR. MOYER: So it's two parts?

DR. WARREN: So steroids are given to negate the adverse events. But a patient who's already on steroids, does it make any sense to put them on these agents or are they completely negating the effect?

MR. MOYER: I'd ask Dr. Feltquate to address that question as to the clinical experience. He's our clinical monitor responsible for the adult

program.

DR. FELTQUATE: David Feltquate, global clinical research. As I understand it, there are really probably two quick questions that you're asking there. One of them is, do corticosteroids prior to initiating treatment have an impact on clinical outcome? And I wasn't sure. Was there a second question about patients receiving corticosteroids in the course of treatment and whether that will have an impact?

DR. WARREN: If patients are on steroids, can they have an effect?

DR. FELTQUATE: For nivolumab trials, we've been excluding patients that are on high doses of corticosteroids, so we don't have direct information of that for -- another checkpoint in ipilimumab, there have been trials on patients with brain tumors, and they were separate cohorts. One of the cohorts contained patients who were received corticosteroids. And although the activity, compared to the cohort that was not receiving corticosteroids, was less, there was still evidence

of clinical activity in those patients.

DR. SMITH: Dr. Seibel?

DR. SEIBEL: Could you provide more details about the infusion related reaction and hypersensitivities reactions, particularly timing and if patients were rechallenged?

MR. MOYER: Certainly. Dr. Walker, could you address the safety regarding the infusion reactions?

DR. WALKER: The majority of infusion related reactions and hypersensitivity reactions were grade 1/2 reactions that mostly presented as blood pressure changes. Most of them came after 2 to 3 doses of medication. And most of the patients have been rechallenged successfully, occasionally requiring Benadryl and Tylenol pretreatment.

DR. SMITH: Dr. Casak?

DR. CASAK: So you stated that the occurrence of nivolumab decreasing body weight. However, the proposed dose for the pediatric trial will use the same dose as currently in adults, therefore exposing patients to

higher -- sorry -- so patients would have higher exposures. Could you please comment on that?

MR. MOYER: Yes. I'd ask Dr. Amit Roy, who's our pharmacokineticist, to describe why the approach that we're taking.

Dr. Roy?

DR. ROY: Amit Roy, clinical pharmacology, Bristol-Myers Squibb. So, yes, the clearance of nivolumab does decrease with decreasing body weight. And therefore, dosing on a milligram per kilogram basis is expected to achieve approximately similar exposures in pediatric patients as in adults. The fixed dose we lower in pediatric patients, and the clearance will also be lower in pediatric patients.

MR. MOYER: Does that address your question? You seem to have another --

DR. CASAK: So the dose will be higher basically in smaller kids than in adults.

MR. MOYER: The dose will be higher in smaller kids?

DR. CASAK: The exposure, not the dose.

DR. ROY: So thus far from our pharmacokinetic data in adults, we've seen that over a wide body weight range, we see similar exposures given a milligram per kilogram dose. And because the mechanism of elimination of nivolumab is not fundamentally different in pediatric and adult patients, a milligram per kilogram dose, which in the lower body weight patient will be a lower dose amount, is expected to achieve approximately similar exposures because the clearance will also be lower.

DR. CASAK: Thank you.

DR. SMITH: Dr. Widemann and Dr. Sekeres, and then we'll proceed to the open public hearing.

DR. WIDEMANN: I was wondering if you could inform us a little bit about the time of resolution of adverse events, single agent and the combination? Typically, the adverse events resolve very quickly after stopping an agent.

MR. MOYER: So your question is the timing of when they occurred?

DR. WIDEMANN: How long it takes for these

adverse events to resolve, and they are fully --

MR. MOYER: Dr. Feltquate, could you address the question of resolution of the adverse events after onset?

DR. FELTQUATE: Just a point of clarification. Were you asking for both the combination or just monotherapy?

DR. WIDEMANN: I think I'm more interested in the combination because the incidence was higher. And I was wondering do these adverse events resolve and how long does it take.

DR. FELTQUATE: Sure. Resolution occurs over the course of days, and in some cases as long as many weeks, depending on the severity. So the patients who require corticosteroid treatment, we often find that the symptomatology and the grading decreases over the course of that first week, and there will be full resolution over the course of several weeks.

DR. SEKERES: Thank you. Given the adverse events that have been seen in adults, are there any tumor types or locations you would avoid in the

pediatric population?

MR. MOYER: Any tumor types that we would avoid?

DR. SEKERES: Tumor types or locations of tumors that you would avoid treating?

MR. MOYER: Dr. Namouni, any tumor types that we would avoid or location of tumors that we believe should be avoided, based on our evidence thus far?

MR. NAMOUNI: Thank you. Based on our discussion and collaboration with many investigators in the United States and in the European Union, we are not excluding tumors or settings based on safety at this point. We presented the four tumors that we would like to start with, and then expand based on the knowledge that we will gain from biomarker studies, from some relevant adult data, or from the signal that we would see in the very first safety cohorts in children.

DR. SEKERES: So in other words, if you have like a p-nadir [ph] or synovial in the lungs, the

pneumonitis signals that you're seeing and that we saw with the previous drug wouldn't be concerning?

DR. NAMOUNI: We would be doing this in the context of phase 1, obviously, and would be very carefully assessing patients in this phase 1.

DR. SMITH: Dr. Reaman, last question.

DR. REAMAN: Thanks. Just to follow up on the issue of CNS metastases in patients with melanoma, was there evidence of activity? And is there evidence that this agent as an IgG for antibody actually crosses the blood-brain barrier? And if so, tow what extent?

MR. MOYER: Dr. Renzo Canetta, could you address the question regarding observations of any patients with CNS metastases in the melanoma population and also whether the antibody does cross?

DR. CANETTA: So in the case of nivolumab up to this point, only patients with stabilized CNS lesions have been accrued to the trial. However, in the case of ipilimumab, where the patient population for the phase 3 trials consist of the

patient with stabilized lesion, for that program, we actually conducted a specific trial for patients with active brain metastases for melanoma.

The results are published in Lancet. The first doctor is Dr. Mark Golding [ph] from the University of California, San Francisco. And remarkably there, the efficacy existed and was observed. The longer term effect in terms of survival were similar, actually, to the population with non-active brain metastases. There was a slight difference in outcome for patients who required the steroid treatment because of symptomatic presentation versus those that did not.

The second question for you, does it cross -- I think the answer is in the biology. It doesn't need to cross the blood-brain barrier because, remember, we are targeting the immune system, and the lymphocytes do that.

DR. SMITH: We need to --

UNIDENTIFIED MALE: Before you go, I just have a follow-up question of Dr. Reaman's. In that population of patients who had stable, metastatic

disease to the brain, did you notice any different toxicity profile in that patient population?

DR. CANETTA: No. We actually did conduct a regulatory submission for ipilimumab, quite a number of analyses, including prior use of steroids, concomitant use of steroids. Patients with stabilized lesions often are maintained and tapered on steroids. There was no difference in toxicity. There was no difference in efficacy.

Open Public Hearing

DR. SMITH: Thank you. So we'll begin the open public hearing, and there is some text that I must read.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of

your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open

way, where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair.

So at this time, will speaker number 1 step up to the microphone and introduce yourself? Please state your name and any organization you are representing, for the record?

DR. MASSUCCO: My name is Dr. Anna Massucco, and I'm representing the Cancer Prevention and Treatment Fund. So with that, I'll begin.

Thank you so much for the opportunity to speak today, again, on behalf of the Cancer Prevention and Treatment Fund. My name is Dr. Anna Massucco, and after completing my PhD in developmental biology from Harvard Medical School, I conducted research at the National Cancer Institute. And so I bring those perspectives today.

Our nonprofit organization conducts research, scrutinizes data and the research literature, and then explains the evidence of risks

and benefits to patients and providers. Our president is on the board of directors of the Alliance for a Stronger FDA, which is a nonprofit dedicated to increasing the resources that the FDA needs to do its job. Our organization does not accept funding from pharmaceutical companies, and therefore I have no conflicts of interest.

Pediatric cancers represent a dire, unmet medical need. Several pediatric cancers still cannot be cured, and patients relapse within a few years. Cancer immunotherapy is an area of great excitement and promise for addressing these issues as we seek non-genotoxic strategies for pediatric patients who are uniquely vulnerable to those long-term effects of such treatment. Therapies of this class have some potential to synergize with existing standards of care, which is an essential aspect of the combination therapies ultimately required for curative care. We support the FDA's efforts to expedite medical advances for pediatric cancer patients, but this priority should not come at the cost of safety standards.

Although distinct from the side effects resulting from traditional chemotherapy, nivolumab and MK-3475 do have significant risks. Three deaths occurred in the trials of nivolumab in advanced malignancy patients, adult patients, due to uncontrolled pneumonitis. Out of 296, 1 percent. Grade 3 and 4 adverse events occurred in 14 percent of these patients.

The assertion that pediatric patients will tolerate this drug comparably to adults relies on a single ongoing study of a different drug, ipilimumab, and only 6 patients under the age of 12 to date. Well, ipilimumab is also an immunomodulatory drug. It is a distinct agent with a different mechanism of action. Thus, critical safety data cannot be extrapolated from these studies.

The Bristol-Myers Squibb studies do not include any preclinical data in non-adult primates. As the Bristol-Myers Squibb briefing document acknowledges, these drugs may have different and more pronounced effects in pediatric patients since

their main system is still developing. I have four recommendations that I respectfully suggest you consider.

In the Merck preclinical studies, toxicity was evaluated in primates at an age roughly comparable to a young toddler, but the plan here calls for trials in infants as young as 6 months of age. Before pediatric studies began, longer term preclinical studies of MK-3475 and nivolumab should be performed in primates at comparable stages of development so that these patients are not exposed to greater safety risks than those already observed in adults.

Until such studies are conducted, I hope you will urge the FDA to oppose the Bristol-Myers Squibb plan to initiate pediatric studies in nivolumab immediately at the adult dose of 3 mgs per kg without any further preclinical studies.

Secondly, the Bristol-Myers Squibb plan also includes pediatric trials using the combination of nivolumab with ipilimumab. This combination resulted in markedly increased toxicity in

preclinical studies, which were conducted for only 4 weeks and also in the study of adult humans.

In the melanoma study in adults, almost half the patients, 49 percent, experienced grade 3 or 4 events. This percentage is higher than the 40 percent who showed beneficial clinical response. In other words, the risks outweighed the benefits with more patients experiencing serious side effects than benefitting. Combination treatment was discontinued in 21 percent of patients in this trial due to these adverse events.

Other studies have indicated that these serious adverse events are not always reversible. For example, 2 percent of patients taking ipilimumab in a phase 3 trial had hypopituitarism, which can be permanent. This condition requires long-term hormone replacement therapy, but even that will not completely eliminate significant health risks. Tragically, those risks would be exacerbated in young patients who are still developing. Longer preclinical studies are needed to evaluate safety before it be ethical to begin

combination trials with ipilimumab.

Number 3. The Bristol-Myers Squibb briefing document emphasizes the importance of early detection for management of adverse events. High doses of corticosteroids will undoubtedly be required to control drug related adverse events, and this could be dangerous in children in particular.

We agree with FDA that the long-term effects of immune modulation should be carefully considered in the context of a pediatric population. The pediatric study plan does not yet delineate specific steps for rapid clinical detection and management of these events, which will be more difficult in these patients. It is essential that those specific steps be delineated before research is conducted.

Lastly, as the FDA has noted, the appropriate combination and sequence of use of these agents with other non-overlapping mechanism of action agents should be a priority consideration in the ongoing studies in adults. We also agree

with the FDA that the threshold of PD-L1 expression used for patient selection should be modified for combination therapy where PD-L1 expression could be induced. Therefore, a lower initial threshold of expression may still identify a responsive patient population and that the planned biomarker studies explicitly address this possibility. This will ensure that these agents are used to the greatest effect in all patients who need them.

In conclusion, the four steps I outlined above will help reduce the risks to children with pediatric cancer and also help ensure that these therapies will reach the patients most likely to benefit from them. Thank you.

Questions to the Subcommittee and Discussion

DR. SMITH: Okay. Thank you for your comments.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before

the committee as well as the public comments. And we will begin the panel discussion portion of the meeting. Although this portion is open to public observers, public attendees may not participate except at the specific request of the panel.

Dr. Reaman from FDA will introduce the questions.

DR. REAMAN: Thank you. So we have a series of five questions. There's actually been some discussion of some of these, but I think there's an opportunity to expand on some of that discussion.

Question number 1 is, please consider the potential role of the checkpoints in immunoregulatory T cells in children and how their pharmacological manipulation might be applicable in the treatment of molecule cancer and possibly lead to synergism with currently used drugs.

I think we've had a little bit of comment about utilizing these or integrating these into standard regimens, but we haven't been very specific about what standard regimens. So we have certainly touched upon the issue of perhaps the

inhibitory effect of corticosteroids, but are there other drugs that we might want to avoid using in combination, or are there drugs that we might specifically select to consider in evaluating combination therapies?

DR. SMITH: Dr. Warren?

DR. WARREN: So I think this gets back to this morning's session where we don't know what's the minimum immune function that's necessary in order to have responses to these agents. And if you have a concurrent therapy that has effects on the immune system, either boosting it or immunosuppressive, it may definitely affect the response to these agents. So I think there is definitely room for some more preclinical testing to see what's the minimum function you need in order to get a response.

UNIDENTIFIED MALE: I would step back a bit before we talk about what we could combine it with and focus on the need to identify are there the pediatric equivalence of melanoma or non-small cell lung cancer, or renal cancer, within the pediatric

population, either anti-PD-1 alone or the combination of nivolumab and ipilimumab.

If there is, then there are all sorts of combinations that could be considered. But really, that has to be the first point. And I think, obviously, we can be hopeful that in a refractory population, we're going to identify those populations that are responsive. But I think it's obviously far from certain yet that that will be the case.

DR. REAMAN: The purpose of the question was not really to design studies looking specifically at combinations, but rather are there -- and I certainly understand Dr. Warren's concern. I'm not sure what preclinical experiments, models, could actually be used or perform to address the situation to the point that you might want the answer about the absolute minimum number of competent T cells required to see a response. But are there situations where we think something might synergize or be synergistic with these, given the mechanism of action? Or are there drugs, either

given in combination or given prior to exposure to these, that we may want to avoid in the evaluation or testing, or at least consider their potential impact as we evaluate both efficacy and toxicity?

So that's really --

DR. WARREN: Well, I think you bring up a good point in that is this something you can give with cytotoxic chemotherapy? And we don't have data on that right now. But I think the concern would be is making sure you have T cells around and how your cytotoxic therapy interacts with that.

DR. REAMAN: And I guess that would be a question maybe for both of the sponsors. Are there data to suggest that there's a better or worse response based on patients' immune status or immune function at the time of receiving therapy? Have those investigations even been performed in any of the clinical trial data that's available to date?

MR. MOYER: Renzo can follow. So you're asking about some overall immune status. Is that right?

DR. REAMAN: [Inaudible - off mic.]

UNIDENTIFIED MALE: Yes. I think our eligibility criteria of course exclude patients who have either very severe immune dysfunction or autoimmune issues as well. So I don't think we really have that data.

I think I would take -- again, it goes back to, at the tumor level, of course, we and others do have data that says that if PD-L1 expression is up, there's a higher likely response in both of the histologies we studied.

DR. CANETTA: And I will say that the second aspect that you briefly alluded to is the interaction with other standard treatments in immune systems. There is quite a lot of literature produced mostly by the group of Dr. Zitvogel in France and by Dr. Koukas [ph] in the states, that tested different cytotoxic agents in combination with immunological agents. With probably known conclusive results, certain agents seem to combine better.

The big issue here, one always thought that cytotoxic chemotherapy is a no-no if you are using

an immunostimulating agent. Yet there is an entire different way of thinking that speaks of other modality, not only including cytotoxic chemotherapy but also radiation therapy with the abscopal effect, the exposure of antigen, the presentation of antigen, and the fact that tumor burden reduction might actually facilitate the immunologic approach.

I think the jury is still out. But what is interesting and important to point out is that the appropriate clinical trials are actually now going on, obviously. Initially, indeed, we're doing with them with ipilimumab, but obviously in the future, they will be done with other agents.

DR. SMITH: Dr. Widemann, did you have comment on this?

DR. WIDEMANN: I was just wondering also to consider the timing. And right now this would be given to children with refractory cancers that are very heavily pretreated. And we heard that adults that are heavily pretreated can respond, but a thought would be a different time to -- if these

agents potentially lead to more efficacy.

Also, as Dr. Sondel pointed out, potentially patients that have lower tumor burden or minimal disease, would they have a better outcome, or potentially could this prevent tumor recurrence and be another setting to explore these agents?

DR. SMITH: Ms. Goodman?

MS. GOODMAN: I just have a question whether it would be possible or reasonable to collect data on treatment history for each patient so that there could be a possibility of correlating certain agents with outcomes. Of course, it may not necessarily be powered enough to have a really comfortable p-value, but I think it might provide some information that would be valuable.

UNIDENTIFIED MALE: I would think that studies that are looking at efficacy, it would be appropriate to certainly collect those data. I mean, I think in the early phase studies, where definition of dose-limiting toxicities and defining a recommended phase 2 dose, that may not be the appropriate or the best.

But I'm a little bit concerned because we talk about pretreatment, but when you speak about pretreatment in the pediatric setting, since all of our therapies are so intense and so myelosuppressive, immunosuppressive, what impact is that prior therapy or concurrent therapy going to have on the activity of these agents? So I think it is something that we would need to think about in designing probably later phase studies.

DR. SMITH: I think that really gets to the point Dr. Sondel made that in fact cytotoxic chemotherapy is remarkably effective for a number of different conditions. And so, the relevant question for many of these diseases, given where we are now, is given cytotoxic chemotherapy that's effective and the immune system that's affected by that chemotherapy, then how well does the immunotherapy respond?

Dr. Fingert?

DR. FINGERT: We've been talking about the -- Dr. Canetta mentioned the evolving work that's ongoing to better understand this question

of combining with immunotherapies and cytotoxic therapies. But I'm concerned here about learning from experience from the adult where the same sorts of thinking was applied.

So for example, in common adult indications, like lung cancer, there have been studies with TLR9 combined with standard chemotherapy, where the outcomes actually was worse when you had the combination, more toxic, less activity, more deaths. So that was in a common indication.

When we're talking about pediatrics with rare subsets to move now into a combination with cytotoxics with our current state of knowledge, it concerns me that it would be premature to start to go that route unless there was really much more of a sound basis to build on. To just do it empirically could be using up a lot of patients in rare indications.

DR. SMITH: Greg?

DR. REAMAN: I don't think there's any plan, and I wasn't suggesting that there should be a plan to empirically develop combinations and start

investigating combinations. So it is premature. First of all, we don't know how tolerable these agents are going to be in children, what the effective or optimum biologic dose is in children, and if there's any signal of efficacy in any pediatric cancers.

So I think we need all of that information before we start actively talking about any combinations. But this was really more a question of theoretical concern and the potential impact of prior or concomitant chemotherapy and what that might have on the efficacy of these checkpoint inhibitors.

DR. SMITH: Dr. Armstrong?

DR. ARMSTRONG: Just a couple things. I want to come back on the flip side of that and stress -- I heard from Dr. Sondel very clearly this relationship to tumor burden and response, so a clear plan for being able to link that. And in cases where reduction of that tumor burden is possible, to have a plan for considering that prior to instituting the therapy makes sense, both from a

scientific perspective and also there's a potential benefit to the participants who are in the study. That is confounded somewhat by the cytotoxicity that might be involved in that pretreatment.

The other piece of this is looking at the AEs. And when we're looking at children, we know that many of the adverse events of current therapies aren't seen for a period of time, but those are developmental in nature. And so I raise the question and challenge to have a very good developmental assessment of AEs, not just acute but emerging particular, especially in children under 5.

DR. SMITH: Dr. Goldman?

DR. GOLDMAN: I mean, I certainly agree with what you say. I think the only concern is in a phase 1 setting, the chance of actually collecting any of that data -- unless these are all homerun -- are going to be so minimal.

Going back to Kathy's comment earlier, I was wondering, do you think there should be a minimal immune function panel done as a criteria to be

eligible for the trials?

DR. WARREN: What we do right now is sort of pick an arbitrary number for some of the studies. Say you needed an absolute lymphocyte count of 500, what does that mean? We don't know. CD4? CD8? We just sort of pick it arbitrarily. And so it would be helpful to know if there's a minimum number.

Also, I think -- and correct me if I'm wrong. I think there was a preclinical study looking at ipi and temozolomide, which is lympho-depleting, which showed more activity than ipi alone. Again, you guys correct me if I'm wrong. So we don't know if more is better or less is better.

UNIDENTIFIED MALE: Perhaps again we could get the sponsor's comments on this just in terms -- Alc of 500, is that something that has any plausibility from your perspective in terms of entry criteria for this type of therapy?

DR. CANETTA: Renzo Canetta, BMS, clinical. If I could make three points, number one, on the

biomarker. I think we have evidence that Alc is a good biomarker post-initiation of treatment. There is no correlation between the Alc count before treatment begins and the outcome of treatment with ipilimumab. Again, our experience is limited to ipilimumab.

There have been a number of biomarker tests that have been conducted. We know that there is a reduction in theoretics. We know that there are certain genetic characteristics that are actually related to inflammatory conditions that could relate to a potential effect. But at this moment, I don't think it would be fair to say that we have a pretreatment predictive biomarker, and certainly not the Alc.

The second thing, because it was asked of -- we actually ever conducted -- and again, for ipilimumab -- two fairly large, randomized, phase 2 trials, one in small cell lung cancer and one in non-small cell lung cancer, where we compared standard chemotherapy, standard chemotherapy concomitant with ipilimumab, and standard

chemotherapy where ipilimumab started after two cycles of chemotherapy.

Interestingly enough, in both trials, superiority was shown in terms of progression-free survival, and in one of the two trials with a trending survival as well for the phased approach, which is consistent with reduction of the tumor burden and consistent with presentation advantage. Now, these are randomized phase 2 trials. We're conducting right now randomized phase 3 trials, where we are comparing the standard of care versus the phased type of approach. These trials are ongoing.

Then there was a third question -- I'm sorry -- concerning tumor burden. If you think of the data that have been presented today, and if you think of the effect that checkpoint inhibition exerts in terms of long-term effect, long-term survival, our preoccupation is really to help -- I mean, we rejoice for the results of the long-term survival, but how do we handle the patients on the left part of the curve?

Again, coming with the standard of care may be an approach, and we're exploring it. But the data that was presented today at least indicates the potential that by combining immune agents, we could actually exert the type of tumor burden reduction that might actually help and gain the time to mount a complete immunoresponse to the tumor. That's if it does [indiscernible].

UNIDENTIFIED MALE: We also don't know from our current data set whether there are markers in peripheral blood such as lymphocyte counts that are associated with outcome. Over time as the data set grows, we may learn more. Our hypothesis, though, is that regardless of what's in the periphery, if the tumor shows that there's a preexisting immune response. There are T cells present. There is up-regulation of PD-L1 such that it appears the tumor's responding to a tumor-specific immune response. And then that patient is likely to respond, probably irrespective of what you can observe in the periphery.

DR. SMITH: Thank you.

DR. REAMAN: We can go on to the second question unless there's any comment about number 1. We did hear one example of combination inhibiting multiple checkpoint pathways. Is that a role that has potential in pediatrics? So I think just a brief discussion of that since we don't even have evidence that inhibition of a single checkpoint has a role at this point. But if it does, does combining inhibitors and looking for multiple inhibition make sense? If that makes sense.

DR. SMITH: I comment that obviously this is a extraordinarily active area of research in adult cancers. And it's not just the PD-1 CTLA4 targets, but multiple other targets as well. So I think in pediatrics, we're really going to have to learn from the adults. The ipi/nivolumab combination looks interesting. There are multiple other combinations that are in clinical development or will soon be in clinical development of other checkpoint inhibitors and other immune related targets.

I think that's one of the challenges, is

that today we're talking about these two. But a year or two years from now, there will be three or four other similar agents that we will want to think about for pediatric development. And so it's really going to take a prioritization and a careful learning from the adult experience, and I think a careful interrogation of pediatric tumor tissues to understand what are the most promising ones to move forward in pediatrics.

UNIDENTIFIED FEMALE: Yes, I agree with Malcolm there's such limited data right now, other than the diseases in pediatrics that occur in adults where activity has been shown already. And what you said, Greg, that if you do this in phase 2 studies, you want to at least look at all the potential factors that might impact response that are collective respectfully so that you can then enrich your population from the potential responders. And tumor expression is one aspect, but other immunologic factors or other clinical characteristics that might be important should be looked at.

UNIDENTIFIED FEMALE: It's dangerous to disagree with two very esteemed doctors when all you have is a lowly JD degree. But I just want to say from the parents' perspective, I think we have two goals. One is to save kids who may be diagnosed with cancer in 10 or 15 years. And certainly a very careful, measured approach, starting with the monotherapy, is probably the best way to do that.

The second is to see if we can provide any benefit for children right now who have unmet medical needs and who could benefit from the trials. In that respect, I would argue that there is reason to consider combination therapies. In the Bristol-Myers case, the results and the efficacy is clearly more exciting in some of the combinations you've explored, and query why we can't offer that potential benefit to children who would enroll in trials right now today for the next couple years, the kids who are sick now, understanding that we are losing something in terms of information-gathering.

UNIDENTIFIED FEMALE: Just to clarify, I was not opposing to the pediatric development of either single or combined, but I do think we have to -- many of the studies we do currently are negative, almost all of our phase 2 studies. And one reason maybe is that we are not selecting our patient population appropriately. So with these new class of agents, I think we should try to work hard on maximizing identifying who may respond because these would be the patients that we would like to get access to these --

UNIDENTIFIED FEMALE: If I could just respond. I understand that position, so maybe the response then is to make sure we gather as much data about each patient as possible and that we have an informatics system which will enable us to go back and look at, for example, pretreatment history or other possible biomarkers, rather than, say, starting with the monotherapy.

DR. SMITH: Dr. Seibel?

DR. SEIBEL: We're probably at the point we're too early to look at this, but if PD-L1

expression proves to be a biomarker, then it will be really important to look at those patients that should respond, why they don't respond. Or if they respond, what's the pathway for resistance or what develops because that would support, then, multiple checkpoint pathway inhibitions. We're very early in this process, so there is so much more we need to find out.

DR. SMITH: Dr. Goldman, did you have comments?

DR. GOLDMAN: I actually think it was covered. I mean, it's putting it down to the simplest form, what we've learned from cytotoxic chemotherapy, it's always good to combine agents. It's much more beneficial, but I think a measured approach so we know why we're combining and is important; though I do agree with you that we ultimately need to help the children that are out there right now as well.

DR. SMITH: Right. And I think the fact that the Bristol-Myers proposal is moving to combinations pretty quickly as one of the -- is

sending a signal that this is perceived as something that really should be evaluated quickly in the pediatric setting. And my point was just that this will be one of multiple different combinations that will get signals from the adult cancer experience in the next two or three years.

DR. REAMAN: But I would just stress that whatever combination we might consider moving forward with, that it be done in a measured fashion and with a real rationale, and with enough correlative biology built in prior to and during the study to really address issues to understand why some people don't respond and to help guide us in predicting which patients will in the future.

The third question is please consider the potential impact of different stages of immune maturation as a factor influencing tumor response when using immune cell checkpoint inhibitors. And I think we did have some discussion of that. I think without doing a longitudinal epidemiologic study, we'll probably never have a real answer. But we do think that infants, but perhaps not

neonates -- and that's important these days with FDASIA because we have to make a specific case for why we wouldn't study a new compound in the neonatal population. And I think we have a rationale in this case.

But we do feel, I believe -- as a group, I think there was some consensus that although we would certainly want to follow all of these children for any potential unforeseen and unexpected toxicity, that we would anticipate that a child's and infant's response to these agents should be similar to what's been demonstrated in the adult population.

So number 4. This hopefully will incite some discussion. Please discuss any concerns about the potential for long-term modulation of the immune system and any sequelae that may result and discuss some possible monitoring strategies.

I think although the focus here was on long-term, I think we ought to think about short-term monitoring strategies as well as long-term monitoring strategies, both based on what we've

heard about the adult experience to date and the theoretical pediatric concerns.

DR. SMITH: Dr. Widemann?

DR. WIDEMANN: So one thought could be for the design of the phase 1 component to actually increase the duration of observation for adverse events beyond the typical 4 weeks. Adverse events can occur later, and then to allow dose escalation, that would be one thing for the short term in phase 1.

DR. SMITH: Dr. Sekeres?

DR. SEKERES: Thank you. Is there anything we can learn from the phase 1 trial of ipilimumab? The age range is from 2 to 21, so what happened to the kids who were under the age of 5 with this? How much follow-up do we have? It was initiated in 2008.

DR. REAMAN: I'm not sure that we have anyone here that can actually present those results. We have the published or presented public results that Dr. Canetta presented. But we don't have anyone here who's responsible for those

studies at the NCI I don't think that could update us on that, unless, Brigitte, that's what you're checking.

DR. WIDEMANN: I'm just looking at some data that Melinda [ph] had given me. She's the PI for the study. And in the children that were less than 12 years old at the 5 milligram, there were two patients only. So it's a very small number of patients still, and one patient had grade 2 angioedema. And then on the 10 milligrams in the less than 12 year olds, there were three patients. Only one had grade 3 colitis, and one had grade 3 ALT/AST.

I think based on our experience with an agent, it's very important that investigators conduct these studies that are experienced in immune adverse events and act quickly. I think that's probably the key aspect to this. And when this goes to multiple sites -- because we're most used to treating AEs with receptor tyrosine kinase inhibitors or cytotoxic agents. But I do not recall -- and again, Melinda could speak better for

this -- that the adverse events were more pronounced in the younger patients, but they were only very few.

DR. SEKERES: And we don't have any insight into long-term effects on immune reconstitution or anything in these kids?

DR. REAMAN: This was a phase 1 study, so we don't have a great deal of long-term follow-up information, unfortunately.

DR. SEKERES: But we haven't heard about any kind of opportunistic infections or anything?

DR. REAMAN: I think they were considered as potential adverse events. I don't think there was in excess of those. At least the data that was presented at ASCO last year or the year before didn't suggest that there was an increased incidence of opportunistic infections.

DR. SEKERES: Can I ask just a somewhat related question? There were a bunch of kids enrolled on the phase 1 trial who had types of sarcomas. Do we have any idea if any of them responded? Because there's a focus on sarcomas in

the development plans as well. But if none of these kids responded to ipilimumab, should that even be a focus?

DR. REAMAN: I think it's a focus because it's a major unmet clinical need in pediatric oncology. Again, in a phase 1 study, we usually have insufficient data to support whether something is active in a particular tumor or not. And I think the fact that there were a number of sarcomas, probably reflects the referral population to the pediatric branch where this phase 1 study was performed.

DR. SEKERES: No, I get that. And I'm okay with -- you talked a little bit earlier about an adequate biological rationale for enrolling certain tumor types. And obviously that's the ideal, but I'm also okay given that a lot of responses we've seen to chemotherapeutics haven't necessarily correlated with that biological rationale, taking more of a broad approach to enrolling in a phase 1 study. But then, I guess I wouldn't call out in the development plans sarcomas necessarily. I

would focus it more on responsive tumors in a phase 2 evolution or expansion.

DR. REAMAN: I thought that was actually the plan, was to look at specific diagnoses in the phase 2 setting, and then to develop based on activity in the phase 2.

DR. SEKERES: It's certainly mentioned, but then why call out sarcomas and neuroblastomas other than prevalence?

DR. REAMAN: Because they're the diseases in whom we have the worst long-term survival rates in pediatrics. And they're -- I won't say common, but they're relatively more common than some of the very rare tumors who we usually don't have an opportunity to study.

DR. SEKERES: So I get that. And if we use the adult approach as not necessarily perfect, but as an example, we wouldn't design a phase 1/2 study, where it says, phase 1, we're going to do a catch-all, and then phase 2, we're going to focus on non-small cell lung cancer and other responsive tumor types. We couldn't call that the non-small

cells just because it's prevalent, right? So why in these development plans call out tumors just because they're prevalent with no data about response?

DR. REAMAN: I think the reason to get the data about response is to look at response in selected tumors. So we generally reserve broad-based phase 1 studies solely for the purpose -- although sometimes there are expansions. If we're fortunate enough to see some activity in a phase 1 study, you could expand it for rational purposes to evaluate, in a preliminary fashion, efficacy.

I'm not sure that there is the biological rationale that you're seeking for the development plan here, and we recognize that. I think it's more addressing the unmet need. But it's possible that with more scientific investigation and more genomic interrogation, or immunophenotypic interrogation of archived tumor materials, there could be more of a rationale for looking at the specific tumors. And again, I think these are our

plans. I would suspect that they're amendable plans given the evolution of science going forward.

DR. SMITH: Just one comment, and then Ms. Goodman. And there are translocations, these, and there's evidence for immune response to the translocation protein, fusion proteins, from other studies. They are prevalent. There are worse cancers. And there are potential immunogenic proteins that are in these cancers.

MS. GOODMAN: I'd just like to make -- I'm sorry to interrupt.

DR. SEKERES: I don't want to -- I'll make this my final comment so I don't belabor this too much. But it seems like kids with refractory cancers is a terrible thing, and it seems like it's a finite number as well. The example of the ipilimumab phase 1 study is a good one. And it's also illustrative because it started in 2008, and as of 2012, it had enrolled 26 kids. There aren't a lot out there. So I would just hope that in a phase 2 expansion plan, there was a little bit more of a rationale for even calling these kids out.

Otherwise, they may be without any basis for response to ipilimumab.

MS. GOODMAN: I would just like to give more robust defense to Dr. Reaman's position, which is, to me, I think the more interesting question really is where's the unmet medical need? The question isn't where is this drug most exciting because for some indications, there may be other drugs for which the clinicians working on a particular pediatric indication have other priorities that they want to look at for this group of kids.

My understanding is the sarcoma community has been very excited about this drug, and perhaps that's one of the reasons sarcoma was emphasized. But if so, to me that strikes me as an appropriate decision-making process for the sarcoma community. They've decided now is the time to explore this particular treatment.

So we need to have not only a drug-centric decision-making process here where we ask where can this drug be most -- have the greatest signal and have the most efficacy, but a patient-centric focus

which asks -- we have a very small population for each indication. What's the most interesting question to ask for each population.

DR. SMITH: Dr. Goldman?

DR. GOLDMAN: To address your issue, these are just the realities of people who are actually enrolling patients on phase 1 trials. And that number somewhat reflects that 26 patients accrued over that time, the limitation on the number of sites for that study. So you can't just say it's a slow-accruing trial. You have to look at all the reasons for that. And there are also other competing phase 1 studies for that patient population as well, where patients may not have to travel as far, et cetera, et cetera.

But to go more specifically to question number 4, I think one of the issues about long-term modulation of the immune system is we may need to change some of our definitions of how we follow kids coming off the phase 1 trials. So instead of a 30-day follow-up or until all symptoms we think are drug related have now come back to baseline, we

may want to have a longer observational period. And I think it addresses some of the questions that Dr. Massucco commented on as well.

Now, grant it, I know that many of these patients go on to other trials, and many of these patients may unfortunately leave us. We still could have a longer period of observation for these patients, which would help answer directly question number 4.

DR. SMITH: Dr. Seibel?

DR. SEIBEL: When we were talking about the monitoring for safety or monitoring strategies, I guess, particularly with some of the sarcoma patients since pulmonary metastases are a major site of recurrent disease, we should have some strategies in view of the pneumonitis or to monitor these patients closely because this has come up before with other agents.

DR. SMITH: Dr. Fingert?

DR. FINGERT: So just a comment about the last comment before my question. I just want to remind people there have been similar issues with

other drugs that cause pneumonitis and risk management plans that have included things like looking at finger FI02 for a minimum, because you don't want somebody who's immediately -- my question really has to do with how can we think about, talk about, address the long-term safety and understanding.

Dr. Widemann before looked up some information about very small numbers that have happened in the oncology field. But I'd like to ask the sponsor -- maybe if Bristol-Myers could address this -- should we be thinking and learning from other fields?

So for instance, juvenile RA, there have been registered drugs with long-term follow-up of immunomodulators. Crohn's disease, there have been registered drugs with serious immunomodulators followed long term, studied in children. Are those the kinds of examples where there might be something informative to how we think about providing the right kind of advice, moving forward with this kind of program?

DR. SMITH: Do any of the sponsors want to address that?

DR. CANETTA: Maybe I can offer a couple of --

DR. SMITH: Please identify for the -- please identify yourself.

DR. CANETTA: I'm sorry. Renzo Canetta, BMS, clinical. Maybe I can offer to the panel a couple of set of data that I believe could be useful in this case.

Number one, we followed the patient in our pivotal trial of ipilimumab for a long term, and the data actually had just been published two weeks ago in Annals of Oncology. And we had I believe 74 patients, if I remember correctly, that had been alive in excess of two years. And we followed their safety profile. Very, very interesting, the only predominant side effect that was observed was vitiligo. And we're told by our immunology consultant that that's a good sign because it's a sign of activation of the immune system. We didn't see incidence of autoimmune disease emerging,

again, in adults with melanoma treated with ipilimumab.

So that's the first set of information. The second set of information, we looked at young adults in our entire ipilimumab. Again, I only can talk because that's where the data are. And we identified that 37 patients across the seven trials who had metastatic melanoma,, and at an age of 20 to 30 years of age.

Safety-wise, the incidence -- and this is the incidence not after two years but the overall incidence on study -- was a 54 percent any grade of toxicity and 5 percent grade 3 and 4 toxicity, colitis, so relatively consistent with what has been seen with older patients. Interestingly enough, the long-term survival in this group of young adults was 17 percent exceeding the two-year follow-up, so very consistent with what has been seen in adults.

DR. SMITH: Just one question of you, Renzo, the autoimmune diseases or conditions that develop and reverse slowly would be perhaps the greatest

concern. You mentioned reversibility in your two-year follow-up, but for things like the hypophysitis, can you comment on any that you think are not reversible and comment on the impact that might have?

DR. CANETTA: Yes. Again, in our ipilimumab experience, but then we can comment also on the new experience, the acute immune mediated effect, such as colitis, GI toxicity, et cetera, they are reversible. The only one that we cannot consider reversible are the ones that affect the endocrine system. And they do require hormonal replacement. We have seen that for thyroiditis. We've seen that for hypophysitis. And basically, these are patients that are asymptomatic on maintenance replacement hormonal treatment, but that has to be maintained over time.

DR. SMITH: Dr. Widemann?

DR. WIDEMANN: Just a comment. For phase 1 studies in pediatrics, the median survival is something like 5 months when patients start. So unless we see very good results, we may not really

be able to see the long-term side effects. But if we move this into more frontline therapy, this would be important. And as it relates to the ages, I do think most of the time, we have a hard time enrolling very young patients. And that's something that we desire in phase 1 studies. But if there were concerns, one could easily -- which likely would have been any case. They will enroll two or three patients first that are somewhat older children, and then move to allow enrollment of very young children. And that would address some of the safety concerns.

DR. REAMAN: I guess I was just trying to show a sense of potential optimism here. So the long-term -- or the strategies for long-term follow-up wasn't really addressing patients on phase 1 studies, but with the hope and expectation that these do become part of what might be considered standard therapy for children and what long-term measures.

I think your point about staging the enrollment of patients based on age is frequently

something that we request, require. And I think that would probably be appropriate in this situation. But I guess to address the long-term safety issues, and short-term, would be really monitoring potential endocrine abnormalities, which although certainly somewhat disabling are not an unusual complication in pediatric cancer therapy. We have experience dealing with that, and they can be dealt with I think very effectively.

I also think Dr. Fingert's suggestion about registry, based again on the experience that's been seen with immunomodulatory agents in non-malignant disease and particularly the potential risk for developing therapy-induced cancers, would certainly be something that we could work with sponsors to create in this setting since the mechanism of action is very novel, and short-term as well as long-term adverse events are a bit unknown. So doing registries is certainly something that could be part of a negotiated agreement with industry I think.

DR. FINGERT: If I could respond, Greg, I

wasn't really suggesting registries. And actually, I didn't really mean to talk about so much of a cancer concern. I just was trying to address or ask the Bristol-Myers group if they themselves, since they have experience with these other indications, think that knowing about the mechanism for these cancer treatments, if the experience with these other immunomodulators in young children can be informative and can be something that we can learn from in terms of monitoring in general. I didn't really mean that I have some concern about a rise in cancer risk in the people that get treated.

DR. SMITH: Greg, perhaps just to make an obvious point, these long-term effects and the risk benefit balance, early on, the children will be phase 1/phase 2 trials. Long-term survival likelihood will be very low, and so the issue is reduced. Two years from now or whenever, when we think about moving these potentially to the upfront setting, then we'll have to look very carefully at the pediatric experience, adult experience, and look at where risk and benefit appear to be matched

for some populations where a reasonable proportion of children would be expected to be long-term survivors.

UNIDENTIFIED MALE: Malcolm, I would come back though. I think I raised the issue earlier about at least having a planning strategy for looking forward. We've stumbled in pediatric oncology a number of times because we have initiated something that's been a homerun, and we didn't anticipate the late effect. And we've had to go back and correct it.

This is really an opportunity in a very rare set of tumors to be able to do some thoughtful planning. Some of the adult data that were presented were showing up to two, three years of stable disease. Well, two to three years of stable disease in a 2-year old would provide some very important developmental data on "long-term" outcomes. If we don't have the sponsor think about that, we may come to a phase 3 where we wish we had that, and then we're losing more time.

DR. REAMAN: Okay. We can move on to the

last question, considering the importance of evaluating the correlation of tumor cell PD-L1 expression by specific pediatric cancers with activity. First, how important is that correlation? We may have the perfect storm here with one development plan that enriches and another that doesn't. And then, is there a potential that the combined use of multiple checkpoint inhibitors may prove useful in the setting where there's low PD-L1 expression by specific pediatric cancers? So sort of a two-part question.

DR. SMITH: The point was made that in fact there are some responders who are PD-L1 negative, at least that Bristol-Myers experienced, and there are various caveats of when was the sample collected, how representative is the sample, did it change from if it was a diagnosis sample to the time that a child is now being collected. So our more typical approach, or at least one approach is the approach of saying we start with all-comers, and then we learn from that about whether there is -- whether pediatrics, how much it resembles the

adult situation, how much we can rely on PD-L1 expression to very heavily guide pediatric development.

That's not to say that it's a very attractive option to say PD-L1 expression will treat that and we're going to enrich. The question is how good is your marker for positive predictive value and negative predictive value, and do we really have enough evidence to do that right now for neuroblastoma or rhabdomyosarcoma.

DR. REAMAN: And we probably don't have the evidence obviously, but I think it's important that we do as much as we can to collect that evidence or to at least collect the data so that we can answer these questions.

UNIDENTIFIED FEMALE: So this question is for the sponsors or maybe one of the immunologists. Since we know PD-L1 is not static or likely not static, is there a way to induce it to improve the response?

DR. REAMAN: By using immunotherapy. I guess Dr. Sondel left. But we were talking

earlier, and that probably one way to actually induce PD-L1 is by using some other form of immunotherapy prior to the use of these agents. We don't know if it is sort of self-inducing in patients who have tumors for long periods of time, whether they're responding to any therapy or not responding to therapy. So I think there are multiple unknowns, many unknowns. Everything is unknown. But I think we have to seize every opportunity to ask these questions and to try and answer these questions.

I guess the one piece of information that we would be interested, do you see a problem with not enriching for PD-L1 expression or do you see a problem with enriching initial patient populations for PD-L1 expression? Or is there an opportunity to learn from these two different approaches as to whether or not there may be predictive information that we can glean from PD-L1?

Dr. Rubin, you can --

DR. RUBIN: I think that one thing I wanted to just comment on was I think crizotinib is a

great example of where I think the signal in lung cancer might have been missed if the 1B expansion cohort wasn't enrichment design. It really has to do with prevalence. So I hope we're in the space to be lucky enough where these drugs work broadly across pediatric malignancies, and we don't have to worry about it. But I think in the beginning, we might miss a very active drug if we're not looking potentially for PD-L1 expression.

DR. SMITH: And for the record, that was Dr. Rubin from Merck.

DR. CANETTA: Renzo Canetta, BMS, clinical. Of course, our philosophy is slightly different. We believe that asking prospectively the question for all-comers will provide a more complete answer. I personally believe that we don't have any issue with expecting more activity with a high PD-L1 expression. The question is what about the others. And I believe that our proposal, that encompasses also the possibility to study the combination that may or may not necessarily be affected to the same extent by the PD-L1 expression, I think is an

appropriate way to ask the question. That's what we do as clinical investigators.

DR. SMITH: A point would be we've done trials where we start the initial phase 2 as the kind of open enrollment. And then if the marker negative population doesn't respond, we continue it with a marker positive population. I think I would be concerned if there wasn't some experience, plan, for a marker negative population. There is that plan, and so I think we'll get an answer.

DR. REAMAN: I guess we didn't touch on the issue of combined checkpoint inhibitor approaches in the setting of PD-L1 non-expression. Is that one rationale for using combination approaches, or is there a rationale for combining inhibitors if you don't see? From what I understand of the BMS data to date is that the responses to the combined approach were no different, based on PD-L1 expression. I guess at least that sort of answers the question, but I think we would have to ask the same question in pediatric tumors going forward.

DR. SMITH: So the combination experience is

very positive and certain would warrant some pursuit in pediatrics. My immunotherapy colleagues at CTEP tell me about many other combinations that are in the pipeline. And so again, this will be the first of multiple combinations like this where we will try to follow as quickly as we can behind promising adult leads.

Dr. Fingert?

DR. FINGERT: Dr. Smith, I don't know if I heard you correctly, but I think you said that the combination data to date are very positive.

DR. SMITH: What I was referring to was the melanoma data for the ipilimumab and nivolumab combination that I would characterize as positive, yes.

DR. FINGERT: Okay. Well, I would just remind the panel that I think I would prefer to think of it as interesting or maybe even on the road to promising. But I do have concerns about making too much of a commitment to combinations, either with another immunotherapy or with chemotherapy in the frontline. Nancy Goodman

raised this question earlier; are we really doing -- should we go faster into some combination program of chemotherapy.

I raise the example of the TLR9, which was studied in lung cancer. And Dr. Canetta brought up the very preliminary results that had been out about their phase 2 experience, their going to phase 3. But we have to remember, the phase 2 experience with TLR9 was also very positive. They had improvement in PFS, improvement in OS, and it was published and presented and advocated, and everything. Then when the phase 3 happened, the opposite. The phase 3 results did show worse outcome by combining the immunotherapy with the chemotherapy.

So I just want to say I still have some cautions about overcommitting towards combinations unless we have more late, full data on what all these outcomes are going to show us.

DR. REAMAN: And I'm not sure that there's any commitment to combinations. We've skipped a step here. First we have to find that there's

activity. And if there's activity, that the risk/benefit would warrant continued evaluation.

So I think any discussion of combination, whether it's combination immunomodulating agents or combination of one of these immunomodulating agents with chemotherapy, are all very theoretical and hypothetical. And if we should be so lucky and fortunate that we get to the point of talking about combinations, I think it will only happen when we have a better understanding of what these drugs do as single agents from the standpoint of efficacy and safety.

So we're not committing to anything. And even though we may commit even in a written request for combination studies as part of a long-term development plan, we evaluate the results of these studies in a real-time fashion. And if those plans have to change, they can be amended. And obviously, if we seek too much toxicity or we see no efficacy, then they would be appropriate reasons for amending studies and amending written requests.

UNIDENTIFIED FEMALE: Just a final word as a

mother whose child did die of medulloblastoma, and I considered many phase 1 trials. You know, all these kids are going to die. And from the parents' perspective, what we lose if we go very, very slowly is all the kids who are dying while we're doing monotherapies.

We do have some evidence, which is that in melanoma for adults, for example, combinations are exciting. It's messier science. But on the other hand, we may give a whole cohort of kids a little bit more life. And to me, that's something that should be taken into consideration when we think about when to start combination therapies.

DR. SMITH: Dr. Yao?

DR. YAO: So my intent today was to help answer or clarify any questions the committee had, but I do actually have a very -- it struck me as I've been listening to the conversation -- a question that I'd like to ask the committee that's sort of related to this. And it seems like there's a little bit of tension between old paradigm and maybe new paradigm, the radiation, chemo, or

cytotoxic surgery sort of paradigm, and now immunomodulation.

In the old paradigm, it seems reasonable that you would want to study whoever you could get because the mechanism would likely potentially be effective. As we're moving into this sort of brave new world of immunomodulation and markers that we see in patients or don't see, it seems that there's a little bit more tension created between who might actually benefit and who might not. And that creates this change in paradigm between a phase 1 traditional and a phase 2 is what I'm hearing of the committee.

So I would really like to have the committee maybe discuss a little bit, if there's time, what makes sense in terms of immunomodulation, or what are the differences here that we as regulators and drug developers and investigators and patients have to keep in mind as we're moving into this type of new therapy.

UNIDENTIFIED FEMALE: At least one of the issues I have with all of this is that we don't

know what harm we can potentially cause with these agents. As with any investigational agent, anything can happen at any time, is just what we usually tell the families. But we work under the premise of first do no harm. And so this big unknown of maybe not benefitting anybody by creating undue harm is a little bit scary and gives us pause.

DR. REAMAN: I would just like to suggest that I'm not sure that we're moving from one paradigm to a new paradigm because I think the new paradigm has yet to really be defined. We're moving from a situation that was a little bit more comfortable because we knew mechanisms of action were very basic and crossed many tumor types. But we really haven't defined the new paradigm and the new process.

So I think some of the tension that you hear is related to do you enrich so that you can provide the greatest benefit for the population of patients for whom you think you have the ability to predict they will benefit? But we also know from

experience that some of these new agents are also active in the population of patients that are negative for that predictive biomarker.

So we don't really know how to do this yet I think is some of the tension that you're picking up. But I think in this situation -- and I think anything that we do has to really address that very issue. We need to prospectively evaluate biomarkers, and we have to retrospectively evaluate biomarkers for their predictive ability. And I think we'll have the opportunity to do both there.

Does that sort of answer your question?

DR. YAO: Yes and no. I mean, again, what I think would be interesting to hear the committee discuss is, again, not with all these unknowns, is it reasonable to approach the development of these products as you would a traditional agent, or would there be other information you'd want, for example, before you would absolutely go into a phase 2 population or a phase 1? Is there preclinical information that you would like to have? Those kinds of things. Would these specific

classes -- knowing that, again, the mechanism is potentially more -- or potentially limits the population that would be most likely to benefit.

UNIDENTIFIED MALE: I'm not sure what preclinical information would help here. Immunotherapy preclinical studies for anti-cancer activity are quite challenging. They can be done, but they're challenging. And exactly how they map to the clinical setting is not sure. And I'm not sure what additional preclinical evidence we would want to see right now before we go to phase 1/phase 2. Again, a phase 1/phase 2 population, these are children who the likelihood for long-term survival is low.

The one paradigm that I think is somewhat new here and changing is there's really a push to try to get answers quickly. And rather than the phase 1, and we wait for the phase 1, and then we do the phase 2, and it takes time to get the phase 2 open -- but if we really want to get an answer with phase 1/phase 2 expansion within the context of the same trial -- and I think you saw

here with the Bristol-Myers' presentation, even the addition of a combination as well.

So I think the paradigm models what's happening in adult drug development is to move as quickly as you can to get the answers in terms of anti-cancer activity for specific populations. So that's a bit of the paradigm I see here. We did it with crizotinib. Again, and the answer wasn't known -- and I think to Dr. Fingert's point, the answer wasn't known about crizotinib so clearly. But we were pushing to get the phase 1 study with a phase 2 expansion cohort done. And I think here is the same idea. This looks promising based on adult data, and we, phase 1 with a phase 2 expansion, quickly get an answer, and then be prepared to move to the next agent or to build upon this, depending on the results.

UNIDENTIFIED MALE: Malcolm, I think the other piece of this is that this is not acute lymphoblastic leukemia with 1800 children, 1800 to 2000 diagnosed a year. And so the time pressure really comes in to how long does it take to do a

trial in a sequential fashion. And in order to do that, our typical standard might take us 10 to 15 years to get to a point, and that really adds a little bit to that tension I think that is here because there's a limited number of patients to be able to work with, and their disease is really bad.

DR. SMITH: Do you need any additional feedback from the committee on these topics?

DR. REAMAN: I don't think so. Thank you. I think you've done a great job of providing feedback, unless there's some additional information.

I would like to thank you and the members of the panel for the comments and the insight. And I would especially like to thank both Merck and Bristol-Myers Squibb for their excellent presentations and for the discussion. As I mentioned starting out, I think this was a somewhat precedent setting, having two sponsors present and discuss different compounds, both of which are intriguing, exciting. And there is enthusiasm at least on the part of the agency to see these

developed effectively and efficiently and to do so with the knowledge that this has to be a global development program.

So working with investigators and with our regulator colleagues in other countries, we look forward to some follow-through on what we've heard today. And I think the information and the feedback that we've received will be helpful in developing our written requests. And again, working with the pediatric committee and exchanging concerns, ideas, will be helpful to us, hopefully to you, and most importantly, helpful to patients going forward. So thank you all.

Adjournment

DR. SMITH: Okay. Very good. We will now break for lunch. We will reconvene at 12:45 as planned, so a shortened lunch break, but we'll try to get started right at 12:45. Please take any personal belongings you may want with you at this time. And committee members to remember that there should be no discussion of the meeting during lunch amongst yourselves, with the press, or any members

of the audience. Thank you.

(Whereupon, the subcommittee's morning session was adjourned.)